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COUNTERFEIT BULK DRUGS

HEARINGS

BEFORE THE

SUBCOMMITTEE ON
OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED SIXTH CONGRESS

SECOND SESSION

JUNE 8 and OCTOBER 3, 2000

Serial No. 106–164

Printed for the use of the Committee on Commerce

U.S. GOVERNMENT PRINTING OFFICE
65–846CC WASHINGTON : 2000

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COUNTERFEIT BULK DRUGS

THURSDAY, JUNE 8, 2000

HOUSE OF REPRESENTATIVES,
COMMITTEE ON COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 11 a.m., in room 2322, Rayburn House Office Building, Hon. Fred Upton (chairman) presiding.

Members present: Representatives Upton, Burr, Bryant, Stupak, and Strickland.

Staff present: Alan Slobodin, majority counsel; Anthony Habib, legislative clerk; Chris Knauer, minority investigator; and Brendan Kelsay, minority research analyst/press assistant.

Mr. UPTON. Good morning, everybody.

We have a number of subcommittee meetings and full committee hearings going on, and we expect a number of members coming in the next few minutes, but in the interest of time we will get started.

Today we are here to dissect the issue of the influx of counterfeit bulk drugs. There is an increase in concern that drug ingredients made overseas that are either counterfeit, unapproved or poorly made are entering our Nation's health care system and endangering patients' health and even their lives.

Here is a case in point. Several years ago, 89 Haitian children died after taking cough medicine made with contaminated glycerin traced to China. We may think that tragic events like this can't happen here in our country with its sophisticated regulatory system, but our committee's investigation reveals that our system does have major flaws, and it could happen here all too easily.

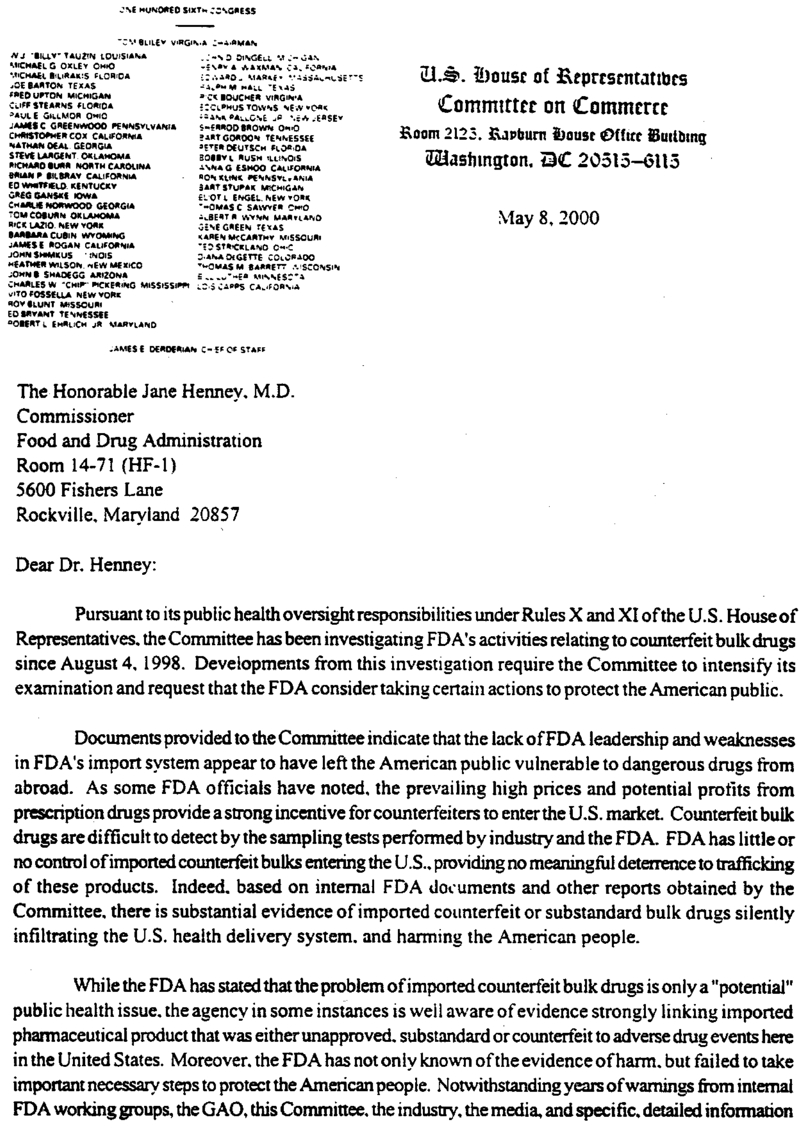
Recently, our committee's investigation revealed that FDA had linked the adverse reactions of 155 American patients to gentamicin sulfate made by Long March Pharmaceutical, a Chinese drug company. It may well be that other patients died from unknown impurities in this drug as well. FDA's own forensic tests showed unexplained discrepancies between the chemical fingerprints of the drug taken from Long March at different times.

FDA's inspection revealed data integrity problems and other serious deficiencies with Long March. Despite FDA inspections in quality control by the U.S. drug companies that use this material, the suspicious bulk drug still infiltrated our health care system without detection. This is just one example of other instances that have confirmed that counterfeit, substandard drug imports are getting into our prescription drug supply and harming patients.

To substantiate our concerns about counterfeit bulk drugs infiltrating our Nation's health care system, I now ask unanimous consent to place FDA correspondence, internal FDA documents and articles on drug counterfeiting into the record documenting the counterfeit bulk drug problem.

Without objection, that is done.

[The information referred to follows:]



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U.S. House of Representatives
Committee on Commerce
Room 2125, Rayburn House Office Building
Washington, DC 20515–6115

May 8, 2000

The Honorable Jane Henney, M.D.
Commissioner
Food and Drug Administration
Room 14-71 (HF-1)
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Henney:

Pursuant to its public health oversight responsibilities under Rules X and XI of the U.S. House of Representatives, the Committee has been investigating FDA's activities relating to counterfeit bulk drugs since August 4, 1998. Developments from this investigation require the Committee to intensify its examination and request that the FDA consider taking certain actions to protect the American public.

Documents provided to the Committee indicate that the lack of FDA leadership and weaknesses in FDA's import system appear to have left the American public vulnerable to dangerous drugs from abroad. As some FDA officials have noted, the prevailing high prices and potential profits from prescription drugs provide a strong incentive for counterfeiters to enter the U.S. market. Counterfeit bulk drugs are difficult to detect by the sampling tests performed by industry and the FDA. FDA has little or no control of imported counterfeit bulks entering the U.S., providing no meaningful deterrence to trafficking of these products. Indeed, based on internal FDA documents and other reports obtained by the Committee, there is substantial evidence of imported counterfeit or substandard bulk drugs silently infiltrating the U.S. health delivery system, and harming the American people.

While the FDA has stated that the problem of imported counterfeit bulk drugs is only a "potential" public health issue, the agency in some instances is well aware of evidence strongly linking imported pharmaceutical product that was either unapproved, substandard or counterfeit to adverse drug events here in the United States. Moreover, the FDA has not only known of the evidence of harm, but failed to take important necessary steps to protect the American people. Notwithstanding years of warnings from internal FDA working groups, the GAO, this Committee, the industry, the media, and specific, detailed information from criminal investigations, the FDA has taken only preliminary steps to gain information on the problem of imported counterfeit drugs. It appears that the FDA has so far failed to take all of the necessary steps to upgrade its import system and to adequately investigate the criminal shipping of counterfeit drugs into the U.S. healthcare delivery system.

The case of gentamicin sulfate illustrates my concerns. Gentamicin sulfate is an antibiotic drug given by injection to treat serious infections such as blood poisoning or inflammation of the heart lining. Suspicions about imported, counterfeit gentamicin sulfate stemmed from FDA's criminal investigation in 1991 involving counterfeit oxytetracycline (an animal drug) purporting to be from Long March Pharmaceutical in Sechuan, China. The investigation eventually implicated a major broker of bulk drugs, Flavine International, and pointed to several possible counterfeit imported drugs such as gentamicin sulfate. In August 1994, in connection with the investigation into counterfeit bulk drugs involving Flavine International, the FDA's Office of Criminal Investigations (OCI) received an OCI-requested package of information from FDA's Center for Drug Evaluation and Research (CDER) Division of Epidemiology and Surveillance. That package of information concerned adverse drug events associated with the administration of gentamicin sulfate and was obtained from FDA's computerized Spontaneous Reporting System (SRS). For the reporting time frame of 1989 through August 16, 1994, the SRS contained 1,974 adverse event reports associated with gentamicin sulfate, including 49 deaths, 251 hospitalizations, and 96 disabilities. The vast majority of adverse events were linked to gentamicin sulfate manufactured by Fujisawa, USA and its Lyphomed Division and Solopak Laboratories. These firms all used the same source for its bulk gentamicin sulfate: Long March Pharmaceutical of Sechuan, China. Although I requested in 1998 virtually all documents relating to the Flavine case and the FDA provided these documents, the Committee has no information indicating what OCI or CDER ever did in 1994 with the data on gentamicin sulfate.

In March 1996, defendants in the Flavine investigation entered guilty pleas pursuant to plea agreements and cooperated with the government. Debriefing of the defendants confirmed that for several years several bulk drugs were counterfeited, including gentamicin sulfate, and sold for use in the manufacture of human prescription generic drugs. (Notwithstanding the guilty pleas and the admissions to federal investigators, FDA failed to de-bar Flavine International and the defendants in the Flavine case. Flavine International continues to be an active broker.) Significantly, an OCI agent wrote the Report of Investigation (ROI) covering admissions by Flavine officials that counterfeits were supplied to the human generic drug industry. However, that ROI made no mention of any planned follow-up to the generic drug companies to make certain no products made from the counterfeits were still on the market.

On May 15, 1996, an OCI agent, involved in the Flavine investigation but who did not write the ROI, wrote a seven-page memorandum to an OCI Special Agent in Charge entitled, "Counterfeit Imported Human Rx Bulk Drugs." In this May 15, 1996 OCI memorandum, the author noted that gentamicin sulfate was one of the drugs identified as a counterfeit human bulk drug supplied by Flavine. The memorandum also noted that "it appears there have been deaths associated with the use of the generic presciption drugs made from the prescription drugs made from the counterfeit bulk drugs supplied by Flavine International." The memorandum summarized the history of counterfeit bulk drug investigations since June 1991; described the threat to the human drug industry; described health hazards associated with the use of FDA procedures for controlling the imported drugs (which results in little control, if any); identified related legal issues; identified the potential magnitude of the problem, i.e., the majority of human generic prescription drugs are made from imported bulk active ingredients; described the financial incentive for the international drug trade to be involved with counterfeits (black market drugs can be half the cost of authentics); and provided some recommended courses for Agency action.

The assessment of the OCI agent was corroborated at about the same time by a memorandum by a U.S. Customs Service agent who was also involved in the Flavine investigation. As a result of the U.S. Customs Service agent's memorandum, the U.S. Customs Service agreed to fund a Counterfeit Drug Initiative. In contrast, the Committee has no evidence that OCI management took any action in response to the May 15, 1996 memorandum, including authorizing joint efforts with the U.S. Customs Service on its Counterfeit Drug Initiative.

However, the concerns about counterfeit bulk drugs were later echoed in other quarters of the FDA outside of OCI. In an August 1996 memorandum, the FDA's Forensic Chemistry Center noted: "We have detected human and animal, bulk and dosage counterfeit pharmaceuticals. . . . We literally have no control over bulk drugs that enter the US . . . Counterfeit or unapproved bulk drugs can unknowingly be received by legitimate dosage from manufacturers and turned into tablets/capsules and sold as legitimate drugs. These drugs can reach anyone including the President."

In 1995, the Forensic Chemistry Center had suggested to FDA Commissioner David Kessler the possibility of establishing an agency-wide initiative related to counterfeit drugs. A number of initial meetings were held, but with varying opinions on how to address the issue, no clear-cut agenda developed. By late 1996, the internal OCI memorandum and other information on counterfeit bulk drugs reached the Commissioner's office, which resulted in a meeting of the Commissioner with other FDA staff on counterfeit or unapproved bulk drugs. At that late 1996 meeting, Dr. Kessler asked that a counterfeit drug working group initiative be coordinated by the Office of Operations. Dr. Randy Wykoff, the Associate Commissioner for Operations, headed the Working Group. During 1997, a series of meetings were held, involving FDA's Office of Regulatory Affairs (ORA) management, various ORA components (including OCI, the Forensic Chemistry Center, and ORA field staff), Center for Drug Evaluation and Research (CDER), Office of Special Investigations (OSI), Office of Chief Counsel (OCC), and others. A work list of potential action items was developed, prioritized, and implemented during 1997. Major actions included communication, training, inspectional activities (as a follow-up to the Flavine case, 15 finished dosage manufacturers were inspected), a pilot study to permit import investigators to access FDA databases, and an authentic database on bulk drugs was started. One of the communication action items involved the FDA (the Mid-Atlantic Regional Office and the Forensic Chemistry Center) and the United Kingdom's Medicines Control Agency (MCA) cooperating and sharing analytical and forensic methodology and associated intelligence on counterfeit bulk drugs.

However, by January 1998, the Commissioner's initiative on counterfeit bulk drugs was terminated. According to an internal FDA memorandum, the initiative was terminated for several reasons: While counterfeit medical products were found to be an issue of significant potential importance, no specific need for a Commissioner's Office initiative was identified. It was felt that the Centers and ORA were the appropriate FDA components to deal with counterfeits. It was also claimed that with the passage of the FDA Modernization Act (FDAMA) in 1997, substantial new, higher priority, responsibilities were being added to FDA. Ironically, on February 5, 1998, around the time the Commissioner's initiative on counterfeit bulk drugs was terminated, Vice President Al Gore and the United Kingdom's Prime Minister Tony Blair honored the FDA-MCA team for its partnership on counterfeit drugs with the Vice President's Hammer Award for improving the performance of the government.

As a result of the termination of the Commissioner initiative, many of the responsibilities from the Commissioner Group devolved to the Foreign Products Working Group. This group was formed to identify foreign active pharmaceutical ingredients and finished dosage forms using a risk management system for sampling under CDER's Drug Product Surveillance program. However, in late 1999 the Foreign Products Working Group was disbanded and the mission of recommending imported bulk drugs for postmarketing surveys was absorbed into the Post Marketing Surveillance Group. On January 27, 1999, you, as the new FDA Commissioner, were briefed on the Counterfeit Drug Initiative. Several general areas where FDA action could be taken to further reduce the risks posed by counterfeit drugs were discussed, mainly an ORA initiative regarding importation of bulk product and several regulatory proposals. To date, very little, if any, of these actions (other than a draft workplan) have been taken. There is no record of any discussion on making meaningful changes to FDA's import admissibility system or on creating a criminal investigative task force with the U.S. Customs Service. Both of these actions would at least prevent or deter some counterfeit bulks from entering the U.S., as opposed to detecting and recalling counterfeits already in the U.S. market.

During the time since 1996 that the FDA implemented some follow-up actions on counterfeit bulk drugs and then proceeded to downgrade the agency's oversight priorities of counterfeit drug imports, the problem of adverse drug events from Long March gentamicin sulfate persisted. In the October 23, 1998 Morbidity and Mortality Weekly Report, the Centers for Disease Control (CDC) and the Los Angeles County Department of Health Services reported a succession of at least 57 moderate-to-severe endotoxin-like reactions (chills, rigors, fever) that occurred in the western United States over an approximately six-month period. These reactions were associated with the administration of endotoxin-contaminated gentamicin for injection manufactured by Fujisawa, U.S.A. As noted previously, Fujisawa's source for gentamicin sulfate was Long March Pharmaceutical.

By September 1998, the FDA Foreign Product Working Group had begun to target the Long March gentamicin sulfate issue. According to the minutes of the September 1, 1998 meeting of FDA's Foreign Products Working Group, it was the consensus of the group to sample imported gentamicin sulfate because it was considered a high risk product with high volume. The justification noted a "substantial amount being imported by Chinese firms; not sure of results from Long March. Fujisawa's source has ADE (Adverse Drug Event) problems."

In November 1998, one of the first hospitals to report the problem (University of New Mexico) again experienced a series of patient reactions when using Fujisawa's gentamicin injection. The hospital reported that no reactions occurred when they used gentamicin made by other manufacturers. Fujisawa, U.S.A. (which was purchased by American Pharmaceutical Partners, Inc. (APP) in June 1998) notified the FDA of an increase in the number of reports of chills, rigors and fever with their gentamicin intravenous product. As of November 19, 1998, APP received 38 adverse event reports involving 66 patients. Subsequent investigation by the CDC and the FDA eventually led to issuance of a Dear Health Professional letter and voluntary withdrawal of gentamicin sulfate by APP on November 30, 1998.

A few sporadic reports were received in early December 1998, generally with APP's product, although two reports were with ESI Lederle's product that also used Long March as the source. In May 1999 FDA was notified of a cluster of adverse events occurring in Denver, Colorado with ESI Lederle's product. Additional reports continued to be submitted, including several clusters of reports of individual institutions. On June 28, 1999, ESI Lederle and, on August 17, 1999, APP, respectively, voluntarily withdrew lots of gentamicin sulfate associated with higher than expected incidence of adverse events. During July and August 1999, the United States Pharmacopeia Practitioners' Reporting Network received five reports, involving eight patients, describing pyrogen-like adverse reactions to gentamicin sulfate injection. Four patients received an ESI Lederle gentamicin product and four patients an APP gentamicin product.

On September 7, 1999, FDA recommended an import alert for Gentamicin Sulfate Active Pharmaceutical Ingredient manufactured by Long March of Sichuan, China. Significant evidence was cited in support of this import alert: A "for cause" FDA inspection conducted August 3-9, 1999 revealed numerous significant deviations from Good Manufacturing Practices (data integrity, process consistency, manufacturing practices and documentation, water system monitoring and control, laboratory controls); Long March was the sole supplier of the Gentamicin API used to manufacture APP Gentamicin for injection which, when administered, resulted in at least 70 pyrogenic reactions reported as Adverse Drug Events; Fujisawa withdrew approximately 66 lots from the market due to the ADEs; FDA laboratory testing revealed one or more vials from six lots of gentamicin for injection manufactutered by APP did not meet the endotoxin specification and each of these lots were manufactured by Long March; on June 15, 1999, ESI Lederle withdrew 20 lots manufactured by Long March which were consistently reactive to endotoxin; APP's rabbit pyrogen testing showed four of nine lots failed the pyrogen test; ESI Lederle concluded three batches of Long March gentamicin were pyrogenic.

In the September 8, 1999 issue of the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, you published a statement concerning endotoxin-like reactions to gentamicin sulfate: "Since the start of 1998, FDA and CDC have received approximately 130 reports of endotoxin-like reactions -- characterized by fever, rigors, and/or hypotension -- following intravenous administration of two brands of gentamicin sulfate. About 70 of the reported cases were temporally associated with once daily dosage of one product that was voluntarily withdrawn from the market in December. The other product, also voluntarily withdrawn, was associated with more than 60 endotoxin-like reactions reported this year. FDA is investigating these cases."

At the December 3, 1999, Parenteral Drug Association (PDA) Annual Meeting, Dr. Mary M. Fanning, Associate Director for Medical Affairs, Office of Generic Drugs, CDER- FDA, presented "Endotoxin-Like Reactions Associated with Once Daily Dosing of Gentamicin, An Off-Label Use." She noted that for gentamicin adverse events May 1998 - August 1999, there were 210 adverse events involving 149 patients; both firms making gentamicin used the same bulk drug supplier (Long March Pharmaceutical); typical reaction was fever and/or chills, rigors or shivering within 3 hours of the start of infusion; however, 3% were severe reactions, including 1 hypotensive shock requiring resuscitation, 1 intubated, 1 pulmonary edema, 2 admitted to intensive care. She had three conclusions: "Etiology traced to multiple problems in the production of the bulk drug including but not limited to endotoxin; Once Daily Dosing in this case unmasked the bulk drug problem; Off Label Use that involves dosing changes may lead to unexpected adverse events due to higher concentrations of impurities or inactive ingredients in a unit dose."

In January 2000, FDA submitted additional adverse event report information on gentamicin to the Committee. Those records showed gentamicin adverse events from May 1, 1999 to January 11, 2000 as follows: 254 total, 17 deaths, and 202 serious events. To the extent the names of companies are identified in the reports, ESI Lederle product was involved in many of these reports. Fujisawa product is also mentioned.

I am concerned that Long March bulk drugs and/or counterfeit gentamicin sulfate from China may still be entering the U.S. healthcare delivery system. First, it is clear that Long March is still motivated to ship gentamicin sulfate into the U.S. notwithstanding the import alert. FDA records show a shipment of Long March gentamicin sulfate was detained in New York on March 1, 2000. Second, FDA's import alert covers Long March gentamicin sulfate but does not appear to reach all Long March products imported to the U.S. even though FDA has identified data integrity and GMP issues that would be applicable to other products. For example, Long March is the approved source for streptomycin sulfate for a U.S. firm. Third, FDA investigations in Fall 1999 indicated that gentamicin sulfate shipped to the U.S. and labeled as Long March appears to have been manufactured by another Chinese firm that FDA has in fact identified. It is a firm that the FDA has never inspected and has no listing. This is confirmed by certain documents that FDA has obtained. (Since this may still be an open matter the Committee will withhold identity of the firm). The suspicion is also strengthened by FDA's forensic evidence that substantiates chemical differences among the various Long March samples of gentamicin sulfate. Nevertheless, there is little evidence that FDA is actively investigating this lead. Fourth, limited FDA laboratory testing indicated similarities between Long March samples and yet another Chinese firm which FDA has yet to inspect and further investigate. (Since this may still be an open matter the Committee will withhold identity of the firm). Fifth, FDA received an allegation in November 1999 that Long March may have sold gentamicin sulfate to a particular foreign country and re-exported to the U.S. Sixth, the Long March import alert can be circumvented by labeling the gentamicin sulfate for non-pharmaceutical use. As a 1999 FDA Work Plan memorandum on counterfeit drugs noted: "While the [FDA's] Electronic Entry Processing System (EEPS)/Operational and Administrative System for Import Support (OASIS) identifies which products are subject to these alerts based on the coding entered into the system by the broker, if the code used varies slightly, or the name of the supplier changes, or the country of origin changes, these items may be released for distribution without any examination." An FDA official has also noted that circumvention is widely known and successful because of the workload and lack of sophistication with many of the import investigators. That same FDA commentator observed: "[T]he Import Alert system is also broken to the point that major basic changes are needed, not a Band Aid."

The serious weaknesses in the import system appear to leave America largely vulnerable to imported counterfeit, substandard, contaminated or poisoned products. The Drug Registration and Listing System provides information on foreign pharmaceutical manufacturers based on the statutory requirement that they list the drug products they ship to the U.S. The Drug Listing System is currently used to determine the admissibility of imported pharmaceutical products. However, anyone can obtain a drug listing. As a draft FDA 1999 Work Plan on Counterfeit Drugs noted:

> "The use of the system as a sole decision maker for admissibility has serious weaknesses. The system does not ensure that authentic sources or authentic material as described in new drug applications is in fact being offered for admission.
> The drug listing database does not interface with the Compliance Status Information System (COMSAT) which provides the acceptable or unacceptable compliance status of foreign manufacturers based on the results of the CGMP [Current Good Manufacturing Practices] inspections. As a result, FDA cannot easily match foreign manufacturers who have "listed" with their compliance status. The Drug Listing database also does not interface with OASIS to assist import officers by automatically comparing manufacturers and pharmaceutical products offered for importation. FDA has initiated a pilot program to provide import inspectors access to the EES [Establishment Evaluation System] system."

As one FDA official noted in response to the draft workplan: "[U]se of EES to partially deal with shortfall may even be optimistic - compounded with the workload and lack of sophistication in much of the import investigator domain... the agency will need to make major changes in order to hope to cope with this growing problem."

For the above-mentioned reasons, I believe there is a sufficient basis to suspect that counterfeit or unapproved drugs, such as gentamicin sulfate, are still entering the U.S. directly from China, or indirectly through European sources.

The public health implications of the FDA's inability to control counterfeit bulk drug imports such as gentamicin sulfate are enormous. As the draft 1999 Work plan noted, counterfeit bulk drugs:

> "pose a real or potential health hazard because their manufacturer is often unknown. The fact that the manufacturer is unknown means that there is no product history. Therefore, the safety and efficacy of the product cannot be assured, the impurity profile is unknown and the age, the storage, the manufacturing environment, or the synthesis of the product cannot be determined. The failure to have a product history is also important because if the counterfeit product is not manufactured in accordance with Good Manufacturing Practices (GMPs) this can negatively impact the quality of the finished product since no amount of finished product testing can build quality into the product. Moreover the failure to have a product history means that research development efforts and the clinical trials done by legitimate pharmaceutical product manufacturers are negated."

In addition, it would be virtually impossible to conduct a recall of defective or harmful product. It could also have direct impact on the safety and effectiveness of approved products because patients might decline to take medicine and suffer adverse events for fear of taking a counterfeit product or a counterfeit drug used in combination with an approved drug. It would also have a direct impact on the integrity of the adverse drug event reporting system.

Given the strong public health interests, please provide by June 22, 2000 a plan to the Committee of how FDA will link admissibility of imports of bulk drugs with GMP compliance and a plan to create a criminal investigative task force with the U.S. Customs Service on counterfeit bulk drugs. In addition, please provide by May 22, 2000:

1. Please detail the actions (and the deadlines for implementing these actions) the FDA will take to minimize the possibility of imported counterfeit gentamicin sulfate from China being shipped into the U.S. For example, will FDA extend the import alert to cover all Long March products? Will FDA investigate firms suspected of manufacturing counterfeit, unapproved or substandard gentamicin sulfate?

2. Please identify all imported bulk drugs currently targeted for FDA sampling and surveillance. Include the name of the manufacturer, the country, all of the criteria used for sample targeting, and the criteria that the individual targeted drug actually met. Please identify all imported bulk drugs where FDA has evidence of suspected counterfeiting. Include the name of the manufacturer, the country, the product, and the basis for suspected counterfeiting (discrepancies in labeling, certificates of analysis, etc.).

3. All records relating to data from the OASIS system on the following: the number of ports of entry into the U.S., the number of FDA import investigators total and at each of port of entry, the number of firms in the official domestic establishment inventory (with a breakout for the number of domestic human drug firms), the number of firms in the official foreign establishment inventory, the number of firms in the foreign establishment inventory that have imported to the U.S. since the beginning of FY 98, a breakdown of the foreign establishment inventory by product category (medical devices, radiological health, biologics, human drugs, animal drugs, animal feed, cosmetics, food, etc.), list of foreign drug manufacturers that have shipped to the U.S. but have no drug listing; the number of foreign drug manufacturers that have shipped to the U.S. but have never been inspected by the FDA (include a breakdown for China and India).

4. Can OASIS import data now be electronically cross-referenced with inspection data from the COMSTAT and OCFITS (Office of Compliance Foreign Inspection Tracking System) databases? If so, provide the number of foreign drug manufacturers exporting to the United States that have not been inspected by the FDA in at least seven years.

5. Of the the total number of foreign drug manufacturers shipping to the U.S. since the beginning of FY 98, what is the most accurate estimate that FDA can provide in terms of percentage of this total that represents the firms that FDA data bases called COMSTAT and OCFITS have information on?

6. CDER collects data from firms that are inspected, and can use OCFITS data to track and analyze trends in types of GMP violations by product, firm, country, etc. Please provide any reports since May 1, 1998 that have used OCFITS data to substantiate trends in GMP violations.

7. In those cases where the shipments are to the U.S. broker that is not the final consignee or to a warehouse not belonging to the final consignee, the final consignee may not be apparent from documents and computer systems at time of entry. Does FDA have any realtime capability at port of entry to determine which domestic manufacturer is receiving the foreign drug product? Assuming that such identification of the final consignee, if needed, could be determined by tracing the product through the distribution channels by investigations of the consignee of record, has FDA ever conducted such investigations since the beginning of FY 98? If so, please provide the name of the product, the name of the broker or agent, the name of the final consignee, and the date of the investigation. Does FDA require a letter from the final consignee finished-dosage manufacturer or enduser authorizing use of the imported product in the New Drug Application? If not, should there be such a requirement?

8. What information is accessible in FDA databases that would indicate a registered foreign manufacturer that is importing bulk drugs to the U.S. is in compliance with Good Manufacturing Practices (GMPs)? Is such information currently accessible in realtime for FDA import investigators at the ports? Is any such GMP information at least stratified by risk, i.e., does FDA even have a product history for sterile injectable drugs imported into the U.S.? If there is no information retained or accessible, please detail FDA plans to develop such a database.

9. How do GMP compliance rates between domestic human drug firms compare with foreign human drug firms? What information does FDA believe is needed to make a valid comparison on compliance rates and is such information collected?

10. All records relating to assessments of FDA information technology for import operations since May 1, 1999.

11. How many notifications of suspect counterfeit bulk human drugs from the Forensic Chemistry Center (or any other component from FDA) have been received by the FDA's Office of Criminal Investigations (OCI) since May 1, 1996? Please provide all records relating to these notifications for closed investigations. Has OCI opened any investigations concerning counterfeit bulk human drugs since May 1, 1996? Please indicate those cases where OCI was the first law enforcement agency to open up the investigation. Out of this total number of opened investigations on counterfeit bulk human drugs, how many resulted in referrals to the Justice Department, indictments, arrests, and convictions? For purposes of this response, "referral" means not only when the United States Attorney's Office (USAO) creates a file or "jackets" the case in their office, but also includes when the USAO declines to prosecute or when the USAO approves electronic surveillance. Please also indicate those cases where other law enforcement agencies are involved. How many of these opened investigations are still open? In how many of these opened investigations did the United States Attorney's Office decline prosecution? How many of these opened investigations were joint investigations with the U.S. Customs Service?

12. What is the criteria that the FDA's Office of Criminal Investigations uses to determine whether it it is appropriate to share information on counterfeit bulk drugs with FDA employees outside of OCI? If the criteria is based on factors such as whether "the information was obtained pursuant to a criminal investigation," please define such factors. Is the appropriateness of sharing this information discretionary to the OCI investigator or is this decided by OCI management? Does OCI have a policy against OCI investigators sharing information of public health concern to other FDA employees? Is this policy in writing? On what date did this policy (either in written form or unwritten form) go into effect? Has this policy ever been altered? If so, what were the changes and when did they go into effect? Under what circumstances, if ever, would such sharing of information by an OCI investigator to an FDA employee be considered an unauthorized disclosure of information? Under what circumstances does the interest in preserving the confidentiality of a criminal investigation outweigh the interests in timely sharing public health information that could save lives and prevent injuries?

13. All records relating to reports provided since January 1, 1999 to FDA's Office of Criminal Investigations on counterfeit bulk drugs.

14. All records relating to communications since January 1, 1999 between the FDA and the U.S. Customs Service concerning counterfeit bulk drugs.

15. Does FDA have an affirmative duty to warn U.S. drug companies who are believed by FDA to be innocently receiving suspected or known counterfeit ingredients? If there is such an affirmative duty and FDA failed to warn, would FDA be liable under the Federal Tort Claims Act?

Please note that, for the purpose of responding to these requests, the terms "records" and "relating" should be interpreted in accordance with the Attachment to this letter.

Thank you for your assistance. If you have any questions, please contact Alan Slobodin of the Committee staff at (202) 225-2927.

Sincerely,

Tom Bliley
Chairman

cc: The Honorable John D. Dingell, Ranking Member

Attachment

ATTACHMENT

1. The term "records" is to be construed in the broadest sense and shall mean any written or graphic material, however produced or reproduced, of any kind or description, consisting of the original and any non-identical copy (whether different from the original because of notes made on or attached to such copy or otherwise) and drafts and both sides thereof, whether printed or recorded electronically or magnetically or stored in any type of data bank, including, but not limited to, the following: correspondence, memoranda, records, summaries of personal conversations or interviews, minutes or records of meetings or conferences, opinions or reports of consultants, projections, statistical statements, drafts, contracts, agreements, purchase orders, invoices, confirmations, telegraphs, telexes, agendas, books, notes, pamphlets, periodicals, reports, studies, evaluations, opinions, logs, diaries, desk calendars, appointment books, tape recordings, video recordings, e-mails, voice mails, computer tapes, or other computer stored matter, magnetic tapes, microfilm, microfiche, punch cards, all other records kept by electronic, photographic, or mechanical means, charts, photographs, notebooks, drawings, plans, inter-office communications, intra-office and intra-departmental communications, transcripts, checks and canceled checks, bank statements, ledgers, books, records or statements of accounts, and papers and things similar to any of the foregoing, however denominated.

2. The terms "relating," "relate," or "regarding" as to any given subject means anything that constitutes, contains, embodies, identifies, deals with, or is in any manner whatsoever pertinent to that subject, including but not limited to records concerning the preparation of other records.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 12 2000

The Honorable Thomas J. Bliley, Jr.
Chairman
Committee on Commerce
U.S. House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

Thank you for your letter of May 8, 2000, regarding the Food and Drug Administration's (FDA or the Agency) activities related to the investigation of counterfeit bulk drugs.

We are preparing a full response to the questions you have posed in your letter. In the interim, however, we would like to respond generally to your conclusion that the American public is "vulnerable to dangerous drugs from abroad" and clarify the regulatory situation as it applies to gentamicin sulfate.

FDA takes allegations of possible counterfeiting or other types of adulteration of drug products very seriously. The overall quality of drug products in this country, however, is very high, and we do not view pharmaceutical quality as a source of major risk. Further, prescription drugs manufactured from imported bulk drugs are not the major source of adverse events. The great majority of adverse event reports in the United States (U.S.) are the result of known side effects of drugs.

It is crucial to distinguish between counterfeit drug products and products that are contaminated or otherwise improperly manufactured. While each of these conditions may pose a threat to public health, counterfeiting is a quite different, and much more rare, occurrence in the drug manufacturing industry. A counterfeit drug includes a drug which identifies itself as the product of a drug manufacturer, processor, packer, or distributor other than the actual manufacturer, processor, packer, or distributor of such drug. FDA investigates both sources of health risks diligently.

While there may be important issues with regard to counterfeit drugs, FDA takes frequent regulatory actions on the full range of manufacturing issues affecting drug quality. FDA has many safeguards in place to detect contaminated or improperly manufactured products, including sample testing, inspection of foreign and domestic firms, and enforcement of current good manufacturing practice (CGMP) standards. These activities will often expose evidence of counterfeiting, where it has occurred.

The Agency is on top of the situation with regard to gentamicin sulfate. FDA began receiving clusters of Adverse Drug Experience (ADE) reports beginning in May 1998 describing pyrogenic reactions (mainly chills or rigor and fever; some with other symptoms) with gentamicin sulfate manufactured by two U.S. establishments.

Two market withdrawals of all lots of gentamicin took place in November 1998 and June 1999, based on the receipt of these reports of pyrogenic reactions. The vast majority of these cases were in patients receiving gentamicin in dosing regimens not approved by FDA. There have been no known deaths reported with these pyrogenic reactions.

Your letter cited 17 deaths reported to the Agency from May 1, 1999 to January 11, 2000. Our analysis has revealed that of the 17 reports, five were duplicative, seven were for foreign incidents, and five were domestic. In only one of the five domestic reports was the manufacturer of bulk gentamicin sulfate identifiable as Long March Pharmaceuticals. This case occurred in July 1999, and was reported to FDA in December 1999. It involved a 20-day old premature male infant suffering from numerous conditions including respiratory syncytial virus. The ADE occurring in the other four domestic cases was renal dysfunction, which is a known side effect of gentamicin. These were seriously ill patients and the cause of death was not stated in these cases. We cannot conclude that Long March bulk gentamicin contributed to these five U.S. deaths, although the relationship cannot be absolutely ruled out.

In August 1999, a FDA inspection team made up of Office of Regulatory Affairs and Center for Drug Evaluation and Research personnel conducted an inspection at the Long March

Pharmaceuticals manufacturing plant in Sechuan, China. Deficiencies were found in the establishment's manufacturing controls; however, no direct link was established between these deficiencies and the ADEs reported on gentamicin sulfate.

FDA issued a Warning Letter to Long March Pharmaceuticals based on deficiencies in CGMP standards and issued an Import Alert in September 1999, recommending that FDA district offices detain without physical examination Long March gentamicin sulfate.

Since the import alert was issued, FDA's Operational and Administrative System for Import Support (OASIS) shows two attempted entries of gentamicin sulfate from Long March Pharmaceuticals. Although one shipment in December 1999, was erroneously entered into the OASIS system as Long March-produced gentamicin, subsequent investigation has revealed that the shipment was not in fact a Long March product. The other attempted entry, in February 2000, was detained and refused admission.

The increasingly global nature of pharmaceutical commerce is stretching FDA's safety net -- foreign inspections are resource intensive, expensive, and more complicated than domestic inspections. Therefore, FDA must continue to be vigilant in its program for detecting all types of problems, which result in the manufacture of substandard drugs. Additionally, we will work cooperatively with Congress to help obtain the resources necessary to adequately perform our oversight functions.

We are working on a full response to the specific questions in your May 8 letter. We will be happy to work closely with the Committee as it examines FDA's regulatory role with regard to imported pharmaceutical products.

Sincerely,

Melinda K. Plaisier
Associate Commissioner
for Legislation

cc: The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 31 2000

The Honorable Tom Bliley
Chairman
Committee on Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

This is in further response to your letter of May 8, 2000, regarding the Food and Drug Administration's (FDA or Agency) activities related to the investigation of counterfeit bulk drugs.

As we stated in our letter of May 12, we are preparing a response to the 15 questions or requests, and will provide it to the Committee as quickly as possible. In addition to the specific requests or questions, you raise a number of allegations and concerns in your letter. We want to respond at this time to a number of those concerns and allegations.

For your convenience, we will restate your concern with a page citation, followed by our response.

"It appears that the FDA has so far failed to take all of the necessary steps to upgrade its import system and to adequately investigate the criminal shipping of counterfeit drugs into the U.S. healthcare delivery system." (Page 2)

Mr. Chairman, FDA does have in place a regulatory system, which includes requirements for ensuring the quality of active pharmaceutical ingredients imported into the United States. The drug approval process requires manufacturers to identify definite sources of active pharmaceutical ingredients for use in manufacturing dosage forms. The identified active pharmaceutical ingredient manufacturer's satisfactory compliance with Good Manufacturing Practice (GMP) regulations is part of the approval consideration for the dosage form.

A dosage form manufacturer using active pharmaceutical ingredients is required to take actions to ensure the quality of these ingredients, including identifying and verifying the source of the materials accepted for manufacture, testing the active pharmaceutical ingredient, and/or utilizing a certificate of analysis verified on a regular basis along with a specific identity test. The finished dosage form manufacturer has the responsibility to use active ingredients from approved sources and to ensure that the active ingredients meet test specifications before incorporation into finished dosage form pharmaceuticals. FDA, as part of its regular drug GMP inspection program, assures during inspections of dosage form manufacturers that these requirements are met.

There certainly are steps the Agency can take to strengthen its foreign inspection/import program, and we look forward to discussing this with the Committee at the June 8 hearing.

"Although I requested in 1998 virtually all documents relating to the Flavine case and the FDA provided these documents, the Committee has no information indicating what OCI or CDER ever did in 1994 with the data on gentamicin sulfate." (Page 2)

While there may not have been any documents to specifically reflect the Agency's actions with respect to gentamicin sulfate, FDA carefully considered the data from 1989 through 1994.

Gentamicin is an aminoglycoside antibiotic that is used to treat serious and life-threatening infections. Although the drug can also be used in healthy individuals for prevention of infection, it is generally given to patients who are very sick. Therefore, with the use of gentamicin sulfate, reports of death and hospitalization are expected due to either the underlying disease and/or infection which is being treated with gentamicin, or to known gentamicin adverse events including renal failure and ototoxicity.

Gentamicin is supplied as premixed intravenous bags (80 percent of the product on the market) and as vials of concentrated drug (20 percent of the product on the market). The adverse events reported for gentamicin involved only the vial manufacturers.

As you know, FDA's Adverse Event Reporting System (AERS) is a spontaneous reporting system. The main utility of a spontaneous reporting system is to provide signals of potential drug safety issues. The system applies to newly-approved drugs whose safety profiles are not yet fully known as well as all marketed products. For older drugs, safety signals sometimes emerge when there is a change in the use profile of the drug or when a product problem occurs, such as the pyrogenic reactions that began to be reported for certain gentamicin products in May 1998. Such reports then trigger further investigation by FDA into a safety issue. Once a safety issue is identified, AERS is again utilized to search for other similar cases; these cases must then be given a hands-on review to determine the significance and/or strength of the potential safety signal. Examining AERS raw data only is not sufficient for this purpose.

You reference 49 deaths that were reported to FDA beginning in 1989 through August 16, 1994. These were raw counts for all reported gentamicin adverse events from any source. When the reports were retrieved and individually examined, it was discovered that one was not a death, nine occurred in foreign countries and seven are duplicate patient cases. Of the 29 U.S. patient cases, the manufacturer of the gentamicin was identified in 13 cases and narrowed down in two additional cases. Renal dysfunction or failure was the gentamicin adverse event in 18 (62 percent) of the death cases. The cause of death was stated in 16 of the cases; the gentamicin adverse event was thought to contribute to the patient's death in ten.

Because gentamicin sulfate is a product used in very ill patients, these reports of deaths, whether due to the underlying disease or to known adverse reactions to gentamicin, were not unusual or more frequent than would be expected. These reports were also consistent with reports received for similar drug products such as Tobramycin.

As FDA was receiving these Adverse Drug Event (ADE) reports on gentamicin, the Agency was also continuing to pursue the Flavine investigation, which included an examination of whether and the extent to which counterfeit gentamicin had been distributed into the manufacturing chain. The information on ADEs was discussed by FDA's Center for Drug Evaluation and Research (CDER), the Office of Criminal Investigations (OCI), the Office of Chief Counsel and the Office of Consumer Litigation at the Department of Justice in order to explore whether it had any bearing on this continuing investigation. Ultimately, it was decided that since all the product was long expired by the time it was discovered by FDA in 1994 (the API was manufactured in 1988 and 1989 and shipped to the manufacturer in 1989), there was nothing the regulatory side of FDA could do at that time. Smith and Nephew (later Solopak Corp.) officials told OCI that the 50 kilogram shipment of suspected counterfeit gentamicin sulfate that was manufactured in 1988 through 1989 had long since been distributed by this company and had also been long since expired. In fact, the company no longer had any samples of this particular shipment on hand.

"Notwithstanding the guilty pleas and the admissions to federal investigators, FDA failed to de-bar Flavine International and the defendants in the Flavine case." (Page 2)

After the company and certain of its officials pled guilty to various charges in March 1996, FDA felt that the penalties imposed on the company and certain managers and employees provided appropriate sanctions and a significant deterrent to future wrongdoing. Flavine Corporation was fined a total of $925,000 for violation of 18 USC 371, while Gerd Weithause, owner of the company, was fined $75,000 and sentenced to 24 months confinement. Seven other employees were given various sentences ranging from a $25,000 fine to pre-trial diversion. It should also be noted that the violative behavior for which Flavine and its officials were convicted were not the types of charges related to product applications for which FDA normally debars companies or individuals.

"Significantly, an OCI agent wrote the Report of Investigation (ROI) covering admissions by Flavine officials that counterfeits were supplied to the human generic drug industry. However, that ROI made no mention of any planned follow-up to the generic drug companies to make certain no products made from counterfeits were still on the market." (Page 2)

The only human drug manufacturer that received what was believed to be counterfeit gentamicin was Smith and Nephews (which became Solopak). A grand jury subpoena issued for that company's records determined that the entire product had been used in the manufacture of finished product that was long distributed and expired by the subpoena date. Follow-up inspections were made at plants that allegedly received other counterfeit bulk pharmaceuticals from Flavine International.

On the bottom of page 2 and top of page 3, you refer to a May 15, 1996 memo from an OCI agent to an OCI Special Agent in Charge (SAC) and a memorandum from a U.S. Customs Service agent. You then state, "As a result of the U.S. Customs Service agent's memorandum, the U.S. Customs Service agreed to fund a Counterfeit Drug Initiative. In contrast, the Committee has no evidence that OCI management took any action in response to the May 15, 1996 memorandum, including authorizing joint efforts with the U.S. Customs Service on its Counterfeit Drug Initiative."

The SAC provided the May 15, 1996 memo to OCI headquarters, and because the memo contained regulatory recommendations, it was forwarded to the Associate Commissioner for Regulatory Affairs for consideration. The memo's recommendation to establish the Metro Washington Field Office as the primary point of contact for counterfeit or unapproved bulk drugs was not considered to be viable or necessary. OCI relied on FDA's Forensic Chemistry Center (FCC), Consumer Safety Officer investigators and inspectors, and the U.S. Customs Service (Customs) to provide information concerning suspect counterfeit bulk drugs entering the U.S. If specific information regarding counterfeit bulk drugs had been developed, it would have been referred to OCI headquarters and criminal investigations would have been initiated in the appropriate venue to be worked jointly with the U.S. Customs Service. At the time, there were neither specific allegations concerning bulk counterfeit drugs, nor any concern of a systemic problem. The Agency decided that a task force for a counterfeit bulk drug initiative was not needed in the absence of actual allegations or cases for such a task force to work.

With respect to the possible authorization of a joint counterfeit drug initiative with the U.S. Customs Service, while Customs did receive some additional funding for the Flavine investigation, at the conclusion of the investigation, the Customs Service agent working the Flavine case was assigned to other matters. Our understanding from Customs is that there were no specific additional leads to follow concerning counterfeit bulk drugs subsequent to the Flavine related investigations. We are also unaware of any later investigative initiatives by Customs regarding counterfeit bulk drugs.

OCI has been in the past, and is currently, fully engaged in working numerous criminal investigations with the U.S. Customs Service involving human and animal drugs, medical devices, and foods. If a counterfeit bulk drug is identified through foreign inspections, FCC's analysis of bulk pharmaceuticals and their packaging, or intelligence information from drug manufacturers or other sources, OCI is fully prepared to work with the U.S. Customs Service and other law enforcement agencies.

In 1997, OCI began to coordinate international efforts aimed at identifying, investigating, and prosecuting pharmaceutical crime through liaison with international efforts that had been formed by the Forensic Chemistry Center. In 1998, OCI formally established a liaison with its international counterparts within the Medicines Control Agency (MCA) in the United Kingdom and the German National Police, Bundeskriminalamt (BKA). This collaborative effort of sharing criminal intelligence has now grown into the Permanent Forum on International Pharmaceutical Crime (PFIPC). This working group is an international enforcement forum aimed at exchanging intelligence and ideas to foster mutual cooperation in combating pharmaceutical crime. The following countries have representatives on this forum: USA, United Kingdom; the Republic of Ireland, Northern Ireland, Spain, Germany, Canada, Singapore, Brazil, Belgium, South Africa, the World Health Organization and the World Customs Organization. The PFIPC meets once a year and facilitates ongoing dialogue among member nations throughout the year.

OCI also meets regularly with the Security Directors of the various pharmaceutical manufacturers. Discussions are held regarding the most productive ways to enhance cooperation by exchanging information and providing assistance during future investigations.

Your letter describes an August 1996 memorandum from the Forensic Chemistry Center and other activities related to establishing an agency-wide initiative on counterfeit drugs, and asserts that "by January 1998, the Commissioner's initiative on counterfeit bulk drugs was terminated." (Page 4)

Then-Commissioner David Kessler did ask the Office of Operations to coordinate an Agency-wide Working Group on counterfeit bulk drugs. However, it was decided by late 1997 that there was no specific need for a Commissioner's Office initiative and that the Centers and ORA were the appropriate FDA components to deal with counterfeits as part of their on-going responsibilities. As your letter acknowledges, a number of actions occurred, including the development of an "action items" list, the establishment of a pilot study to make CDER's Establishment Evaluation System (EES) database available to import inspectors, and the initiation of a cooperative effort with the United Kingdom's Medicines Control Agency.

Other accomplished initiatives from the action items document include the following:

- Specialized training was provided to field investigators in performing API inspections.
- API inspections were conducted at 15 finished dosage manufacturers and three bulk pharmaceutical factories in China as a follow-up to the Flavine investigation and samples were collected for FCC evaluation.
- FDA personnel met with key pharmaceutical company representatives to share information on counterfeiting and related issues.

From 1993 through the present time, the FCC has been an active participant in the Agency's counterfeiting activities. FCC has developed new methodologies to differentiate selected manufacturing sources of the following list of active pharmaceutical ingredients (APIs):

Acyclovir
Albuterol Sulfate
Amoxicillin
Atenolol
Captopril
Cefachlor
Cephalexin
Cimetidine
Cypropheptadine HCI
Diazepam
Dipyridamol
Doxepfin
Doxycycline Hyclate
Erythromycin (various forms)
Ethinyl Estradiol
Fluphenazine
Fluoxetine
Gentamicin Sulfate
Indomethacin
Ketoprofen
Nifedipine
Penicillin (various forms)
Phenytoin Sodium
Pindolol
Ranitidine
Trimethoprim
Verapamil

Some of these methodologies were developed in conjunction with laboratories participating in the international laboratory group. Work on several other APIs is in progress.

Notable outcomes of this analysis program include the following:

During analyses conducted at the FCC and another ORA laboratory, impurities and endotoxins were tested in an effort to assist CDER in investigating and identifying the cause(s) of increased adverse event reports concerning gentamicin sulfate injections. Discrepancies were noted in various samples of Long March gentamicin bulk, which were reported to the FDA District Office leading the follow-up investigation of the gentamicin finished dosage form (the injectable form), as well as to OCI, the Division of Emergency and Investigative Operations (DEIO) and CDER Office of Compliance in January 1999. Higher impurity levels noted in Long March gentamicin compared to other manufacturers were reported during regularly scheduled conference calls concerning the ADEs.

In February of 1999, CDER reviewers were notified by FCC that acyclovir manufactured by a foreign source had high impurities compared to other sources. CDER had been considering the foreign source for possible approval. As a result of the FCC report, acyclovir from this source was not approved for marketing in the U.S.

A database of information on API packaging, labeling, closures, certificates of analysis, etc., being developed by FCC currently lists information for more than 400 APIs from foreign manufacturers. This information is being developed and can be made available to import inspectors and investigators and could provide leads on foreign source suppliers that do not match a known profile.

"During the time since 1996 when FDA implemented some follow-up action on counterfeit bulk drugs and then proceeded to downgrade the agency's oversight priorities of counterfeit drug imports, the problem of adverse event from Long March gentamicin sulfate persisted." (Page 4)

In fact, the adverse events from Long March gentamicin did not occur in the time frame beginning in 1996 that you cite. FDA first learned of an increase in ADEs in 1998 and took appropriate action in responding to those reports. In May 1998, Fujisawa contacted FDA's Office of Generic Drugs about several reports of unusual adverse events associated with Gentamicin used in an off-label dosing regimen. The approved dosage of Gentamicin is 3 to 5 mg/kg/day given in three divided doses. Once daily dosing (ODD), in which a total daily dose of 5 to 7 mg/kg/day is given as a single dose, is an off-label use introduced in the early 1990s to minimize toxicity. Recent surveys indicate that ODD is used widely by up to 75 percent of hospitals in 75 percent of adult, 26 percent of pediatric, and 11 percent of neonatal dosing.

Two clusters of pyrogenic reactions not usually seen with Gentamicin were reported to the MedWatch program between May 1998 and December 1998 involving Fujisawa/American Pharmaceutical Partners (APP) product and between May 1999 and December 1999 involving ESI Lederle product. One hundred fifty-five (155) patients experienced 287 episodes of fever, chills, rigors, shivering/shaking, a rapid heart rate, and high or low blood pressure occasionally associated with other symptoms. These reactions occurred during or within three hours of the infusion and lasted less than three hours in most cases (96 percent). Twelve patients (8 percent) had more serious reactions that led to hospitalization or admission to an intensive care setting. All of these patients recovered uneventfully within 24 hours. Seventy percent (70 percent) of adverse events were associated with ODD, 14 percent with intermediate doses, and 16 percent with the approved dosing regimen.

At the time of the first reports, AERS was checked for reports prior to May 1998 of similar unusual pyrogenic reactions associated with other gentamicin finished drug manufacturers and other aminoglycosides administered as a single daily dose. None were found. Product testing as described below was initiated by FDA's Denver laboratory, and APP voluntarily withdrew its adult formulations of gentamicin in August 1998. FDA inspected the APP manufacturing facility in Melrose Park, Illinois in November 1998. FDA asked the firm to tighten its endotoxin specifications because of the higher potential exposure to endotoxin with the ODD regimen and because of reports of high endotoxin levels in a proportion of the samples tested. The firm complied and lowered its specification to .5 endotoxin units (EU)/mg, which is substantially lower than the USP standard of 1.7 EU/mg.

Because of a small number of reported adverse events towards the end of 1998, in which pediatric vials were used to administer ODD to adult patients, APP voluntarily withdrew its pediatric product as well. APP reintroduced its product using Long March bulk API with the new, lower endotoxin specifications in June 1999. Nine adverse events were reported in August 1999 and the firm voluntarily withdrew all vials manufactured with Long March bulk drug at that time. In October 1999, APP inspected and contracted with a new supplier of gentamicin bulk drug, which was already an approved bulk drug supplier. APP reintroduced Gentamicin manufactured with bulk product from the new supplier in November 1999, and there have been no adverse event reports to date with this product.

In May 1999, similar adverse events were reported in association with the ESI Lederle gentamicin finished product. At that time, AERS was checked again for similar reports of unusual pyrogenic reactions associated with other gentamicin finished drug manufacturers and other aminoglycoside products and none were found. Investigations revealed that ESI Lederle had changed its API supplier to Long March in March 1999 and the adverse events were associated only with lots made with Long March bulk drug. There were no reports associated with product made using ESI Lederle's other supplier, Meiji Seika. Endotoxin testing was not implicated. ESI Lederle voluntarily withdrew its finished product made with Long March bulk in June 1999.

Although McGaw Pharmaceuticals used Long March bulk, no reports were received in association with their product, which provided 4 percent to 5 percent of the gentamicin on the market. McGaw withdrew its product in October 1999.

Throughout this period, beginning in August of 1998, FDA's Denver laboratory performed endotoxin testing on gentamicin samples. Twenty-six (26) lots of Long March bulk drug and three lots of Meiji Seika bulk drug were tested. Of these, only one lot of Long March (#SC-GM 960806) was violative, having greater than the USP specification of 1.7 EU/mg. One of the nine sublots tested had a level of 1.82 EU/mg.

Forty-seven (47) lots of finished product were tested, 28 from APP, 16 from ESI Lederle, 2 from Steris, and 1 from McGaw. Six lots of APP finished product associated with the 1998 adverse events were found to be violative. Rabbit pyrogen testing performed by an outside contractor was unconclusive.

As FDA proceeded with this series of tests over a 15-month period, the results were consistent with the adverse events that had been reported to FDA and confirmed the course of corrective actions that the Agency had undertaken. A timeline of adverse event reports and actions taken by the Agency is enclosed.

"I am concerned that Long March bulk drugs and/or gentamicin sulfate may still be entering the country. First, it is clear

that Long March is still motivated to ship gentamicin sulfate into the U.S. notwithstanding the import alert." (Page 6)

As we stated in our May 12 letter, since the Import Alert on gentamicin issued on September 7,1999, FDA's Operational and Administrative System for Import Support (OASIS) shows two attempted entries of gentamicin sulfate from Long March Pharmaceuticals. Although one shipment in December 1999 was erroneously entered by the broker into the OASIS system as Long March-produced gentamicin, subsequent investigation has revealed that the shipment was not, in fact, a Long March product. This entry is the subject of an ongoing investigation. The other attempted entry, in February 2000, was detained and refused admission.

"Second, FDA's import alert covers Long March gentamicin sulfate but does not appear to reach all Long March products imported into the U.S. even though FDA has identified data integrity and GMP issues that would be applicable to other products." (Page 6)

The OASIS system shows only two entries for dehydro streptomycin bulk product for possible human use from Long March since September 1999. There have also been several shipments of oxytetracycline HCL and neomycin sulfate, which were declared for animal use. FDA's investigation into the data integrity and GMP issues at Long March, as well as the firm's inadequate response to the August 1999 inspection, has caused the Agency to revisit the status of other Long March products. The FDA is considering whether to extend the import alert to other Long March products.

"Third, FDA investigations in Fall 1999 indicated that gentamicin sulfate shipped to the U.S. and labeled as Long March appears to have been manufactured by another Chinese firm that FDA has in fact identified." (Page 6)

In September 1999, as part of the follow-up to the gentamicin ADE investigation being coordinated by CDER, the New Jersey District collected samples of Long March import entries from an import broker. Records obtained revealed that some of the gentamicin sulfate entered as Long March was actually manufactured by another API manufacturer, which is not an FDA-approved manufacturer of gentamicin sulfate or any other human or veterinary drug. Also, preliminary analysis of samples of three lots labeled as that of the other API manufacturer and assumed to be manufactured in 1999 suggests this gentamicin sulfate more closely resembles Long March gentamicin than that from other manufacturers. These matters are the subject of an ongoing investigation which was described to your counsel, Mr. Alan Slobodin, by FDA staff in a May 23, 2000 telephone conversation. Follow-up investigations at the consignees to identify the eventual end-users are ongoing.

"Fourth, limited FDA laboratory testing indicated similarities between Long March samples and yet another Chinese firm which FDA has yet to inspect and investigate." (Page 6)

Results of the testing done by FCC on gentamicin sulfate API from Long March show that there are unexplained discrepancies for certain lots when samples are collected from different locations, including from Long March's retained material. In these instances, there are significant differences in impurity levels and chromatographic patterns obtained by both liquid and ion chromatography for gentamicin allegedly from the same lot. Also, there are at least two as yet unidentified impurities in Long March gentamicin that are undetectable or at very low levels in gentamicin from other sources.

The FCC findings are a part of an ongoing investigation by FDA enforcement components, which also was described to Mr. Slobodin in the May 23 telephone call.

"Fifth, FDA received an allegation in November 1999 that Long March may have sold gentamicin sulfate to a particular foreign country and re-exported to the U.S." (Page 6)

This allegation is currently the subject of an ongoing investigation.

You raised a number of issues regarding the ability of the OASIS system to alert import inspectors to potentially counterfeit drugs or to fully implement import alerts. (Pages 6 and 7)

As you know, the OASIS system began as a pilot program in the Seattle District in 1992. It interfaced with the Customs Automated Commercial System (ACS), screened entries (using ACS) and provided the initial operational support to FDA users. The interface with ACS and the screening subset of the system (known as EEPS) was implemented nationally by June 1995, and use of the OASIS system by industry became mandatory in December 1996.

The baseline of the current version of OASIS with full basic operational functionality was implemented nationally by October 1997. The system has undergone continuous improvement of operational support. A major change in September 1999 moved screening from ACS to OASIS and expanded screening to cover all data elements.

If the information entered in the OASIS system is complete and accurate, the system will identify situations where a drug product has been sold first to a buyer in one country and then re-exported to the U.S. However, if a broker attempts to conceal information, including that which would indicate a re-export, then OASIS, as a filer-driven system, may not alert the import inspector to that situation. While legitimate re-export is a fairly common practice, we do not believe that circumvention of import requirements through intentional misrepresentation of information entered into OASIS is widespread.

"For the above-mentioned reasons, I believe there is a sufficient basis to suspect that counterfeit of unapproved drugs, such as gentamicin sulfate, are still entering the U.S directly from China, or indirectly through European sources." (Page 7)

The FDA has a number of systems in place to assist the Agency in identifying counterfeit products from any API manufacturers that ship products to the U.S., as well as identifying firms for foreign inspection, including those in China. These systems include domestic and foreign inspectional surveillance activities, the establishment of an API profile database, and activities associated with FDA's import operations. Currently, foreign firms are selected for inspection using a risk-based evaluation which includes GMP surveillance and compliance information, volume of product shipped to the U.S. and a for cause perspective.

For cause inspections originate from information generated by OASIS or import operations review, forensic analysis by FCC, statutory inspections, OCI investigations, notification by international regulatory authorities and/or trade complaints.

Firms designated for surveillance are identified by using a four-tiered approach developed by CDER and ORA:

(1) Firms warranting inspection subsequent to previous

significant violative findings;
(2) Firms that manufacture sterile products not inspected within the last three years; and
(3) Firms that manufacture non-sterile products and not inspected within the last five years; and
(4) All other facilities, including contract laboratories.

ADE driven assignments are based on Center assessment of the reported event, frequency, severity, and product involved. The purpose of postmarketing ADE surveillance is to ensure that industry is appropriately reporting such incidents and to obtain information on rare, latent, or long term drug effects not identified during premarket testing. We will also be doing trending in this area.

In an effort to improve FDA's ability to detect and prevent counterfeit and unapproved APIs from entering the U.S., the FCC has implemented a short-term action plan to establish an API profile database that will be used to provide detailed information about authentic APIs when compared to suspect products.

Mr. Chairman, we want to assure you that maintaining the safety and authenticity of imported drug products remains a priority for FDA. We look forward to discussing this with you at the upcoming hearing and working with you and others in the Congress to ensure that this goal is met.

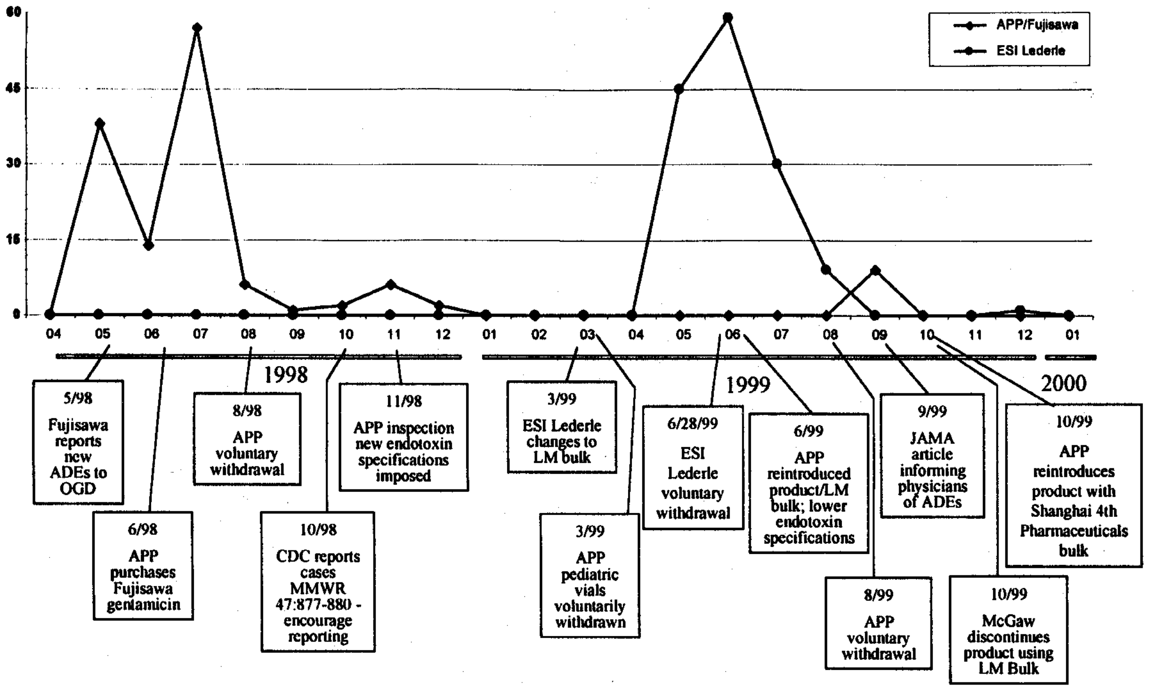
Sincerely,

Melinda K. Plaisier
Associate Commissioner
For Legislation

Enclosure

cc: The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce
House of Representatives

Gentamicin Adverse Drug Event Timeline



5/98 Fujisawa reports new ADEs to OGD

6/98 APP purchases Fujisawa gentamicin

8/98 APP voluntary withdrawal

10/98 CDC reports cases MMWR 47:877-880 - encourage reporting

11/98 APP inspection new endotoxin specifications imposed

3/99 ESI Lederle changes to LM bulk

3/99 APP pediatric vials voluntarily withdrawn

6/28/99 ESI Lederle voluntary withdrawal

6/99 APP reintroduced product/LM bulk; lower endotoxin specifications

8/99 APP voluntary withdrawal

9/99 JAMA article informing physicians of ADEs

10/99 McGaw discontinues product using LM Bulk

10/99 APP reintroduces product with Shanghai 4th Pharmaceuticals bulk

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN -2 2000

The Honorable Tom Bliley
Chairman
Committee on Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

This completes our response to your letter of May 8, 2000, regarding the Food and Drug Administration's (FDA or Agency) activities related to the investigation of counterfeit bulk drugs.

For your convenience, we have restated the 15 questions and requests, followed by our response.

1) **Please detail the actions (and the deadlines for implementing these actions) the FDA will take to minimize the possibility of imported counterfeit gentamicin sulfate from China being shipped into the U.S. For example, will FDA extend the import alert to cover all Long March products? Will FDA investigate firms suspected of manufacturing counterfeit, unapproved or substandard gentamicin sulfate?**

FDA has investigated and continues to investigate firms suspected of manufacturing and/or importing counterfeit gentamicin sulfate. As a result of the Agency's ongoing evaluation of activities related to Long March Pharmaceuticals, FDA has decided to broaden the import restrictions to all bulk drugs produced by that firm.

FDA is considering a number of program enhancements to better detect and act against counterfeit, unapproved or substandard active pharmaceutical ingredients (APIs). With regard to gentamicin sulfate, these enhancements include:

- collecting samples and conducting identity tests on bulk drugs labeled or declared as other than gentamicin sulfate

- and offered for import with consignees who are known end users of gentamicin sulfate;
- inspection of gentamicin sulfate end users and their agents to examine the documentation of sales and shipments of bulk drug substances;
- reconciling inventories and shipments of gentamicin sulfate drug products manufactured at the end user; and
- collecting samples and performing identity tests on bulk drugs at the end user with a physical description similar to gentamicin sulfate.

The Agency has developed a strategic plan to address many of the issues surrounding the importation of bulk drugs and to establish procedures that would allow us to follow-up on all suspect products regardless of country or product. Implementation of a plan developed by FDA's Office of Regulatory Affairs (ORA) and the Center for Drug Evaluation and Research (CDER) to improve FDA's ability to detect and prevent counterfeit and unapproved API's from entering the United States drug supply has begun. The plan will also help define the scope of the problem and make it more difficult for counterfeiters to operate.

The recommendations regarding the Agency's regulation of counterfeit and unapproved APIs include the following:

- Develop a strategy for the inspection of U.S. agents/brokers and conduct inspections,
- Conduct inspections of selected finished dosage manufacturers with regard to APIs,
- Provide additional training to our drug inspector cadre
- Provide for collaboration with the international laboratory group on counterfeit and unapproved drugs,
- Provide investigators with access to database systems that support anti-counterfeiting efforts --
- Meet with representatives from the pharmaceutical industry,
- Analyze and evaluate samples at the FCC.

Continued and full implementation of the initiative is dependent on identification of additional funds and Full Time Equivalents (FTE) for Fiscal Year (FY) 2001.

2) Please identify all imported bulk drugs currently targeted for FDA sampling and surveillance. Include the name of the manufacturer, the country, all of the criteria used for sample targeting, and the criteria that the individual targeted drug actually met. Please identify all imported bulk drugs where FDA has evidence of suspected counterfeiting. Include the name of the manufacturer, the country, the product, and the basis for suspected counterfeiting (discrepancies in labeling, certificates of analysis, etc.).

A list of drugs currently targeted for FDA sampling and surveillance is provided at Tab A. At this time, FDA has no substantial evidence of counterfeit drug importations.

3) (Provide) All records relating to data from the OASIS system on the following: the number of ports of entry into the U.S., the number of FDA import investigators total and at each port of entry, the number of firms in the official domestic establishment inventory (with a breakout for the number of domestic human drug firms), the number of firms in the official foreign establishment inventory, the number of firms in the foreign establishment inventory that have imported to the U.S. since the beginning of FY 98, a breakdown of the foreign establishment inventory by product category (medical devices, radiological health, biologics, human drugs, animal drugs, animal feed, cosmetics, food, etc.), list of foreign drug manufacturers that have shipped to the U.S. but have no drug listing; the number of foreign drug manufacturers that have shipped to the U.S. but have never been inspected by the FDA (include a breakdown for China and India).

There are approximately 310 ports of entry in the United States established by the U.S. Customs Service. Because many metropolitan areas have multiple ports, there are 196 "port areas." Based on OASIS data for FY 2000 to date, 172 of these port areas have one or more FDA regulated entries per week.

In FY 2000, FDA has a total of 254 FTE positions allocated for field investigational operations, of which 68 FTEs are allocated to human drugs.

As of February 2000, FDA's domestic Official Establishment Inventory (OEI) contains records for 114,700 firms, including 17,600 human drug firms (this includes manufacturers, as well as repackers, labelers, and other non-manufacturing concerns). The number of domestic establishments that are eligible for statutory inspections is 6,500.

There are approximately 168,830 firms in FDA's foreign inspection establishment inventory, which includes all FDA regulated products. Of this number, 6,030 are drug manufacturing firms (excluding OTC manufacturers).

A total of 6,030 foreign drug manufacturers have imported to the U.S. since the beginning of FY 1998. A total of 1,234 foreign bulk drug manufacturers have exported to the U.S. since the beginning of FY 1998.

A breakdown of the foreign establishment inventory by product category is provided at Tab B.

FDA does not have a list of foreign drug manufacturers that have shipped to the U.S. but have no drug listing. This would require an interface between the Drug Registration and Listing System and OASIS. FDA is currently working on the technical issues that need to be resolved to achieve such an interface.

The number of foreign drug manufacturers that have shipped to the U.S. but have never been inspected by the FDA is approximately 4,600. The number of such firms located in China is 623 and the number located in India is 409.

4) Can OASIS import data now be electronically cross referenced with inspection data from the COMSTAT and OCFITS (Office of Compliance Foreign Inspection Tracking System) databases? If so, provide the number of foreign drug manufacturers exporting to the United States that have not been inspected by the FDA in at least seven years.

The Office of Compliance Foreign Inspection Tracking System (OCFITS) was designed and implemented within CDER's Office of Compliance in the fall of 1994, as a stand-alone database to track receipt and processing of foreign inspection reports. OCFITS contains inspection data on foreign drug manufacturers that have been inspected for Good Manufacturing Practice (GMP) compliance since the database inception (5 years). OCFITS has about 850 firms in it.

The Compliance Status Information System (COMSTAT) is maintained by ORA and contains an assessment of foreign and domestic firms that manufacture, assemble, repack or relabel drugs or devices, based on the results of GMP inspections.

OCFITS and COMSTAT are not electronically linked to OASIS. However, information from these databases is made available to ORA inspection divisions for developing enforcement strategies and as part of the Agency's routine compliance activities, including the issuing of import alerts used by import inspectors.

5) Of the total number of foreign drug manufacturers shipping to the U.S. since the beginning of FY 98, what is the most accurate estimate that FDA can provide in terms of percentage of this total that represents the firms that FDA databases called COMSTAT and OCFITS have information on?

The most accurate estimate FDA can provide is 18 percent.

CDER's Office of Compliance (OC) has initiated a project of identifying for surveillance inspection foreign firms that have not been inspected. The first two lists provided to ORA covered firms in China and India. In addition, OC is leading the European Union Mutual Recognition Agreement, Pharmaceutical GMP Annex negotiations for determining the equivalency of foreign regulatory systems. Our objective for successful negotiations include the generation of foreign GMP inspection information which can be relied on to ensure GMP compliance on foreign drug products being shipped to the U.S. and where FDA GMP inspections have not been made.

6) CDER collects data from firms that are inspected, and can use OCFITS data to track and analyze trends in types of GMP violations by product, firm, country, etc. Please provide any reports since May 1, 1998, that have used OCFITS data to substantiate trends in GMP violations.

A set of charts generated from OCFITS showing trends in GMP violations for FY 1998 and FY 1999 is provided at Tab C.

We do not have reports which relate GMP violations with product, firm or country. OCFITS contains the profile classes covered during each foreign inspection and codes for the most significant GMP deficiencies noted in the inspection. The system does not correlate profile classes with the GMP deficiencies when more than one profile class is covered.

7) In those cases where the shipments are to the U.S. broker that is not the final consignee or to a warehouse not belonging to the final consignee, the final consignee may not be apparent from documents and computer systems at time of entry. Does FDA have any real time capability at port of entry to determine which domestic manufacturer is receiving the foreign drug product?

No, FDA does not have real time capability at port of entry to determine which domestic manufacturer is receiving the foreign drug product.

Assuming that such identification of the final consignee, if needed, could be determined by tracing the product through the distribution channels by investigations of the consignee of record, has FDA ever conducted such investigations since the beginning of FY 98? If so, please provide the name of the product, the name of the broker or agent, the name of the final consignee, and the date of the investigation.

FDA has a number of investigations underway in which we trace back to the final consignee. Because these are ongoing investigations, we are unable to provide information for the record at this time. If the Committee would like further information, we would be happy to discuss how we can accommodate your request without compromising our investigations.

Does FDA require a letter from the final consignee finished-dosage manufacturer or end user authorizing use of the imported product in the New Drug Application? If not, should there be such a requirement?

At this time, FDA does not require a letter from the final consignee, finished-dosage manufacturer or end user authorizing use of the imported product in the new drug application. Such a requirement may be useful. We believe

FDA has the authority to require the information by regulation.

We have gained experience with the workings of the distribution channels for these products and the legitimate needs of the industry, and we should be able to express requirements for this aspect of the industry without establishing an unnecessary burden or inhibiting trade. We are evaluating the process needed to establish such requirements.

8) What information is accessible in FDA databases that would indicate a registered foreign manufacturer that is importing bulk drugs to the U.S. is in compliance with Good Manufacturing Practices (GMPs)? Is such information currently accessible in real time for FDA import investigators at the ports? Is any such GMP information at least stratified by risk, i. e., does FDA even have a product history for sterile injectable drugs imported into the U.S.? If there is no information retained or accessible, please detail FDA plans to develop such a database.

The Import Alert system, not a database, is used to convey GMP status information to the port inspector. Import Alert 62-05 instructs field office personnel to detain automatically any sterile drug product unless FDA has inspected the manufacture and found it to be acceptable for GMP. Import Alert 66-40 informs the field office personnel of firms whose products are to be detained automatically because FDA considers them to be unacceptable due to the deficient conditions and practices in the firm.

In addition, the compliance status of any foreign firm inspected is available to field office personnel in the COMSTAT database.

We believe the current systems have served enforcement purposes well, but they will be improved when the foreign manufacturer registration requirement is implemented fully, the registration data becomes available in a database, and our objectives in the MRA negotiations are met.

9) How do GMP compliance rates between domestic human drug firms compare with foreign human drug firms? What

information does FDA believe is needed to make a valid comparison on compliance rates and is such information collected?

Compliance rates for foreign drug establishments for fiscal years 1998 and 1999 are as follows:

Classification	FY 1998	FY 1999
No Action Indicated	30%	33%
Voluntary Action Indicated	65%	59%
Official Action Indicated	5%	8%

Compliance rates for domestic drug establishments for Fiscal Years 1998 and 1999 are as follows. (Note: these numbers represent all domestic drug inspections, many of which are not API manufacturers.)

Year	Classified Inspections	Violative Inspections	% Violative
1995	3,458	676	19.5%
1996	3,320	564	17.0%
1997	3,402	709	20.8%
1998	3,318	554	16.7%
1999	2,991	487	16.3%

10) (Provide) all records relating to assessments of FDA information technology for import operations since May 1, 1999.

There have been no assessments of information technology for import operations since May 1, 1999.

11) How many notifications of suspect counterfeit bulk human drugs from the Forensic Chemistry Center (or any other component from FDA) have been received by the FDA's Office of Criminal Investigations (OCI) since May 1, 1996? Please provide all records relating to these notifications for closed investigations.

OCI has been notified by different FDA components of four incidents involving suspect counterfeit bulk drugs. OCI received one unsolicited notification from industry for a total of five notifications. Records relating to these notifications are provided at Tab D.

> **"Has OCI opened any investigations concerning counterfeit bulk human drugs since May 1, 1996?"**

Yes. OCI conducted preliminary inquiries for each of the five notifications it received involving suspect counterfeit bulk drugs. After preliminary inquiries were conducted, OCI established that three of the five notifications were unfounded, so OCI did not open cases based on those notifications. OCI did open the other two cases for preliminary investigation. Those cases are identified as: 00-KCK-705-0054(P)/Sechuan Tetracycline and 98-NYN-723-0090/Northeast #6. Further investigation revealed that 00-KCK-705-0054(P)/Sechuan Tetracycline did not involve counterfeit bulk drugs, and that FCC's suspicions of counterfeit in 98-NYN-723-0090/Northeast #6 were unsubstantiated because CDER was unable to support an action based on the impurities found in FCC's tests.

> **"Please indicate those cases where OCI was the first law enforcement agency to open up the investigation?"**

In both cases, OCI was the first and only law enforcement agency to open an investigation.

> **"Out of this total number of opened investigations on counterfeit bulk human drugs, how many resulted in referrals to the Justice Department, indictments, arrests, and convictions? For purposes of this response, "referral" means not only when the United States Attorney's Office (USAO) creates a file or "jackets" the case in their office, but also includes when the USAO declines to prosecute or when the USAO approves electronic surveillance."**

None of these investigations resulted in referrals to the Department of Justice.

> **"Please also indicate those cases where other law enforcement agencies are involved."**

None of these investigations involved other law enforcement agencies.

"How many of these opened investigations are still open?"

All of these cases are closed.

"In how many of these opened investigations did the United States Attorney's Office decline prosecution?"

None of these investigations were referred to the United States Attorney's Office for prosecution.

"How many of these opened investigations were joint investigations with the U.S. Customs Service?"

None of these investigations were joint investigations with the U.S. Customs Service.

12) What is the criteria that the FDA's Office of Criminal Investigations uses to determine whether it is appropriate to share information on counterfeit bulk drugs with FDA employees outside of OCI? If the criteria is based on factors such as whether "the information was obtained pursuant to a criminal investigation, " please define such factors.

In any OCI case including counterfeit bulk drug cases, if OCI's investigation reveals a continuing risk to public health, OCI will notify the appropriate FDA regulatory staff. Due to legal restrictions placed on the dissemination of grand jury material under Federal Rule of Criminal Procedure 6e, certain information cannot be disseminated to anyone who is not on the 6e list. Accordingly, when cases involve significant public health issues, OCI works with the United States Attorney's Office and the courts to include the appropriate regulatory staff on the 6e list so information may be shared.

"Is the appropriateness of sharing this information discretionary to the OCI investigator or is this decided by OCI management?"

OCI criminal investigators frequently work closely with FDA Consumer Safety Officers and other regulatory personnel on specific cases. In those cases, OCI would routinely share information with the CSO, and the CSO may be included on the Rule 6e list. If the investigation did not involve regulatory personnel and information was developed by an OCI field office concerning a risk to the public, the OCI field office would pass information to the local District Office and to OCI headquarters. OCI headquarters would make the proper notifications at the headquarters level.

"Does OCI have a policy against OCI investigators sharing information of public health concern to other FDA employees? Is this policy in writing? On what date did this policy (either in written form or unwritten form) go into effect? Has this policy ever been altered? If so, what were the changes and when did they go into effect?"

No. The conduct of criminal investigations necessarily involves discretion and OCI does not routinely discuss open investigations. In order to protect the public health, however, OCI has often revealed to other FDA employees the existence of a criminal investigation and some of the information obtained therein, and will continue to do so as circumstances warrant.

"Under what circumstances, if ever, would such sharing of information by an OCI investigator to a FDA employee be considered an unauthorized disclosure of information?"

OCI would never consider the release of vital public health information to FDA personnel to be an unauthorized disclosure of information, provided the law and the court did not prohibit the information from being shared.

"Under what circumstances does the interest in preserving the confidentiality of a criminal investigation outweigh the interests in timely sharing public health information that could save lives and prevent injuries?"

Under no circumstances does the interest in preserving the confidentiality of a criminal investigation outweigh the interests in timely sharing public health information that could save lives and prevent injuries.

13) (Provide) all records relating to reports provided since January 1, 1999 to FDA's Office of Criminal Investigations on counterfeit bulk drugs.

There are five e-mails that led to the opening of two

Preliminary cases, which have now been closed. FDA investigation resolved these suspect counterfeit matters with no actual counterfeit bulk identified. These emails are provided at Tab D.

14) (Provide) all records relating to communications since January 1, 1999 between the FDA and the U.S. Customs Service concerning counterfeit bulk drugs.

This information is provided at Tab E.

15) Does FDA have an affirmative duty to warn U.S. drug companies who are believed by FDA to be innocently receiving suspected or known counterfeit ingredients? If there is such an affirmative duty and FDA failed to warn, would FDA be liable under the Federal Tort Claims Act?

FDA is not aware of any such affirmative duty under federal law. Even if such a duty can be found under other law, FDA believes it likely that the decision to provide or not provide such information would constitute a discretionary act for which immunity is not waived by the Federal Tort Claims Act.

That said, as a matter of policy the Agency has and will continue to provide information on counterfeit ingredients to manufacturers in order to protect the public health. For instance, during the investigation of Pharmaceutical Basics Incorporated and Flavine International, the Department of Justice and FDA learned that forged Certificates of Analysis (Certificates) were being used to hide the fact that unapproved bulk carbamazepine was being imported into the country and used in the generic version of the drug. Once FDA found out that forged and counterfeit Certificates were being used, we immediately notified the approved manufacturer of the bulk drug that its product and Certificates were being counterfeited and forged, thus allowing the approved manufacturer to communicate this information to its licensed distributors and to others that received the approved manufacturers product.

Thanks again for your continued interest in this issue. We look forward to discussing this with the Committee at the hearing on June 8th.

Sincerely,

Melinda K. Plaisier
Associate Commissioner
for Legislation

Enclosures

cc: The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce
House of Representatives

TAB A

FY 2000 ACTIVE PHARMACEUTICAL INGREDIENT (API) SURVEY PRODUCTS: JUSTIFICATION, MANUFACTURERS TARGETED, AND SELECTION CRITERIA

Acyclovir sodium

Justification

Suppliers of drug substance have different impurity profiles.

Manufacturer(s) Targeted

Solchem Italiana, Italy
Heumann Pharm, Germany
Ranbaxy Labs, India
Omnichem, Belgium

Albuterol Sulfate

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted

FDC LTD, India

Amantadine HCl

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted

Northeast General Pharm., China

Amantadine HCl

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted

Northeast General Pharm., China

Amoxicillin and Amoxicillin Trihydrate

Justification

Large volume of sales and many overseas suppliers

Manufacturer(s) Targeted

SmithKline Beecham, U.K. and Singapore
Ranbaxy Labs, India
Bristol Myers Squibb, Italy

Bupivacaine HCl

Justification

Not surveyed for a long time

Manufacturer(s) Targeted

Nordic Synthesis, Switzerland
Boehringer Ingelheim, Germany

Captopril

Justification

It's an ACE inhibitor; challenging USP assay; degrades rapidly.

Large volume of sales and many overseas suppliers.

Manufacturer(s) Targeted

Egis, Hungary
Farmhispania, Spain
Medichem, Spain
Wockhardt, India
Novopharm, Ontario, Canada

Cefaclor

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted

Ranbaxy Labs, India

Cefotaxime Sodium

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted

Lupin Labs, India

PAGE 4

Dipyridamole

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted

Shanghai #6 Pharm. Factory, China

Guaifenesin

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted

Xin Xin Pharm., China

Lidocaine HCl

Justification

Not surveyed for a long time; complaints received concerning lack of anesthetic effect.

Manufacturer(s) Targeted

Delta Synthetic, Taipei Heinen, Taiwan
Societa Italiana, Italy

Loratadine HCl

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted
Morepen Labs, India

PAGE 5

Methocarbamol

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted

Xin Xin Pharm., China

Methoxsalen

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted

Franco India Pharm., China

Pentoxyfylline

Justification

Product has not been surveyed for a long time

Manufacturer(s) Targeted

Plantex, Israel
Orion, Finland
Chemagis, Israel
Secifarma SPA, Italy

Theophylline

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted

Shandong Xinhau Pharm. Factory, China

Timolol Maleate

Justification

Inspectional evidence indicates need for sampling

Manufacturer(s) Targeted

FDC LTD, India

Vancomycin HCl

Justification

Reported adverse reactions and potential counterfeit problems

Manufacturer(s) Targeted

Lupin, India
Alpharma FCD, Hungary
Dumex Alpharma, Denmark

TAB B

Foreign Manufacturers - FY 99
OASIS-Based OEI

Product	**Foreign Firms**
Other Foods	73,967
Seafood	12,922
LACF	10,661
Cosmetics	11,394
Human Drugs	9,734
Biologics	2,211
Animal Drugs & Feeds	3,652
Devices & Rad Health	44,290
Total	**168,831**

Human Drugs		**Animal Drugs/Feeds**		**Biologics**	
-OTC	2,776	-Animal Rx drug	162	-Biologic Products	546
-Rx	4,534	-Animal Bulk drug	86	-Blood/Plasma & Blood Ranking Reagents	1,486
-Bulk Drug	1,248	-Animal Feed	2,952		
-Other Drug	1,176	-Other Feed/Drug	452	-Misc. Biologic	179
Total	**9,734**	**Total**	**3,652**	**Total**	**2,211**

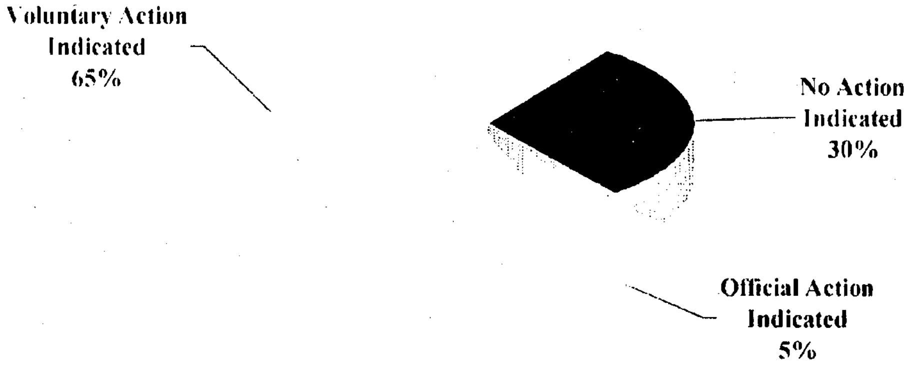
Cosmetic Manufacturers	**11,394**
Seafood Manfacturers	**12,922**
LACF Manufacturers	**10,661**
Other Food Manufacturers	**73,967**
Device Manufacturers -	**24,547**
Rad Health Manufacturers	**19,743**

Total # of foreign manufacturers - 168,831
Total # of countries w/manufacturers - 231

TAB C

Foreign EIR Final Classifications
Fiscal Year 98

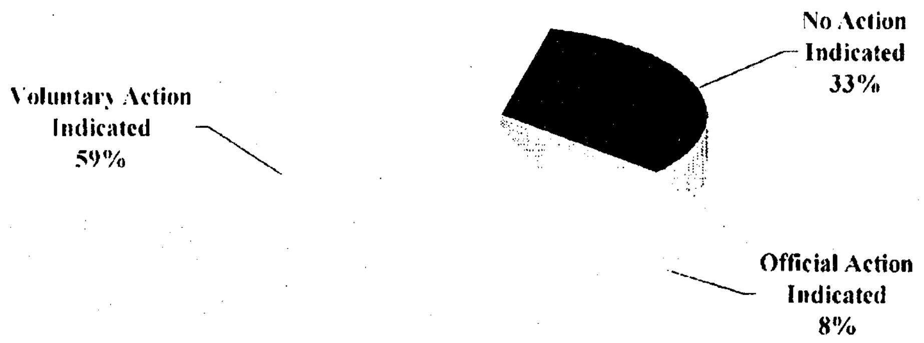
Inspection Reports Reviewed = 259



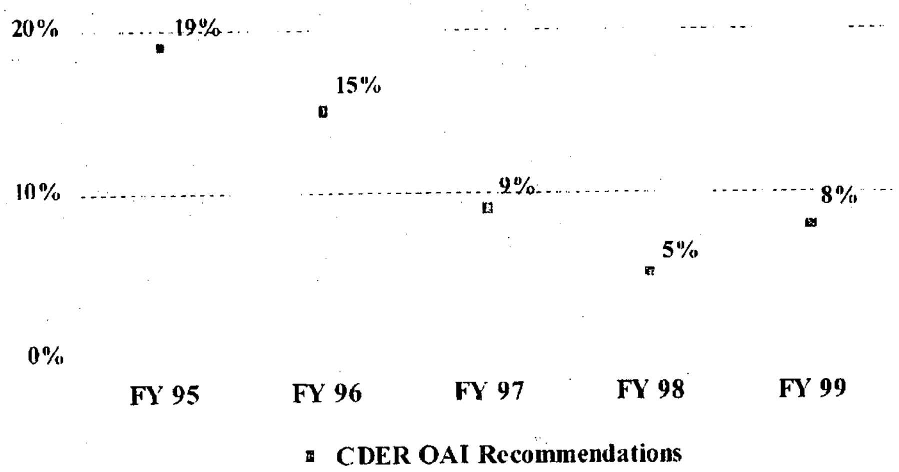
Source: FY 98 international inspection reports reviewed by CDER's Foreign Inspection Team

Foreign EIR Final Classifications
Fiscal Year 99

Inspection Reports Reviewed = 214



Source: FY 99 international inspection reports reviewed by CDER's Foreign Inspection Team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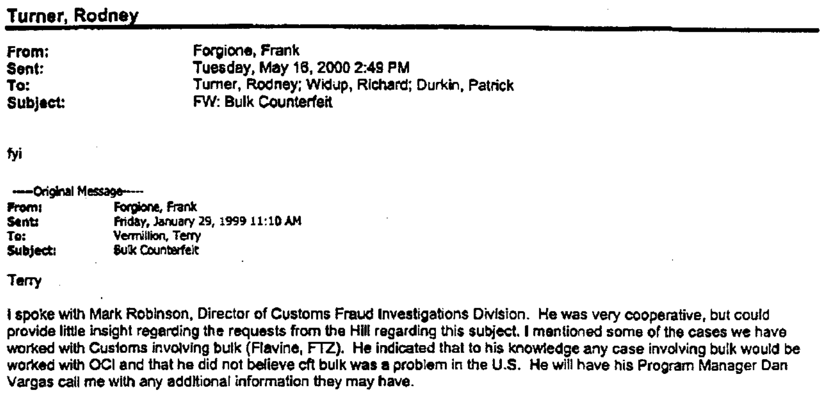
Tab E



Turner, Rodney

From: Forgione, Frank
Sent: Tuesday, May 16, 2000 2:49 PM
To: Turner, Rodney; Widup, Richard; Durkin, Patrick
Subject: FW: Bulk Counterfeit

fyi

-----Original Message-----
From: Forgione, Frank
Sent: Friday, January 29, 1999 11:10 AM
To: Vermillion, Terry
Subject: Bulk Counterfeit

Terry

I spoke with Mark Robinson, Director of Customs Fraud Investigations Division. He was very cooperative, but could provide little insight regarding the requests from the Hill regarding this subject. I mentioned some of the cases we have worked with Customs involving bulk (Flavine, FTZ). He indicated that to his knowledge any case involving bulk would be worked with OCI and that he did not believe cft bulk was a problem in the U.S. He will have his Program Manager Dan Vargas call me with any additional information they may have.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN 6 2000

The Honorable Tom Bliley
Chairman
Committee on Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

This is in follow-up to our letter of June 2, 2000, related to the investigation of counterfeit bulk drugs. As you may know, on June 5, 2000, officials from the Food and Drug Administration (FDA or Agency) met with Committee staff to discuss the hearing on June 8. At that meeting, it came to our attention that it would be helpful to clarify some of the information we provided in our June 2 letter.

Specifically, on page 3, in response to your question 3, we stated that "In FY 2000, FDA has a total of 254 FTE positions allocated for field investigation operations, of which 68 FTEs are allocated to human drugs." We would like to point out that the 254 FTEs are allocated for field **import** operations **for all program areas.** As we discussed, our field investigators work on a broad range of product issues and are not dedicated to one product. The 254 FTEs spend approximately one-quarter of their time doing drug work, resulting in the "68 FTEs allocated to human drugs."

On page 8, in response to question 9, we provided compliance rates for both foreign and domestic drug establishments. While the information we provided is accurate, we provided it in different formats. Staff requested that we provide the same information in identical formats. That information is below:

Compliance rates for foreign drug establishments

Classification	**FY 1998**	**FY 1999**
No Action Indicated	30%	33%
Voluntary Action Indicated	65%	59%
Official Action Indicated	5%	8%

Page 2 - The Honorable Tom Bliley

Compliance Rates for Domestic Establishments

Classification	**FY 1998**	**FY 1999**
No Action Indicated	42%	41%
Voluntary Action Indicated	41%	42%
Official Action Indicated	17%	17%

Thanks again for your interest in this issue. If you have further questions, please let us know.

Sincerely,

Jarilyn Dupont for
Melinda K. Plaisier
Associate Commissioner
for Legislation

cc: The Honorable John Dingell
Ranking Minority Member
Committee on Commerce

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
Public Health Service

MEMORANDUM

DATE: April 28, 1999

NOTE TO: John Taylor

FROM: Stephanie R. Gray

SUBJECT: Counterfeit Drugs

Attached are Office of Compliance/CDER's comments. Additional comments may be coming.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Memorandum

Date April 23, 1999

From Director for HB Acting Dir.
Division of Manufacturing & Product Quality, HFD-320

Subject Counterfeit Drugs
Memo-Comments

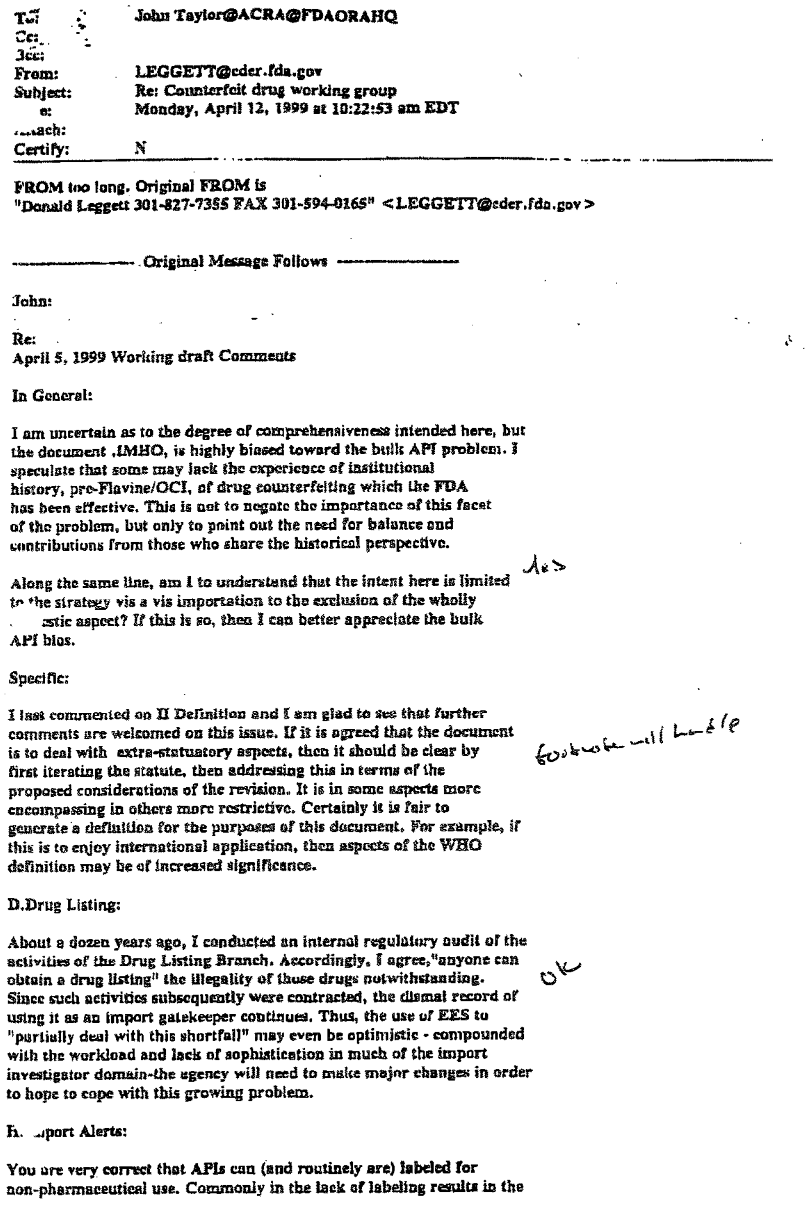
To Director 4/28
Office of Compliance, HFD-300

I have the following comments and suggested lead on each action item.

A. Regarding meetings with Representatives from Foreign Governments and Industry, Joe Phillips and Fred Fricke already have an established lead in meeting with foreign government representatives on this issue. These leads and contacts should continue. It is not a formalized agency workgroup. If we were to formalize the workgroup under this workplan proposal, I would suggest Center representatives join the group including Compliance Officers from HFD-320 and 330, an Investigator from ORA and an analyst from both CDER and ORA.

In terms of industry meetings, I surmise that OCI would interact with the security officials at the firms. Our CGMP inspections currently do not instruct coverage for counterfeit drugs and resources are very limited for the program. Realistically, expanding our routine inspectional coverage to cover counterfeit issues would involve the assignment of resources to this task. Only then could we have a meaningful program with both government regulatory authorities and industry. Any efforts to startup a more formalized program now, given our current state of coverage, would not prove fruitful unless we can find more motivation for industry to report these problems to us.

B. I recommend this program continue under the leadership of HFD-330. Analysis by FCC of samples by non-official methods may provide good investigative leads but are difficult to serve as the basis for regulatory action. NE RL is undertaking the task to validate these methods and HFD-320 has met with OPS & NE RL on this effort. Greater coordination is needed for the efforts of NE RL and FCC and I recommend the Division of Field Science in ORA become involved with HFD-320 in developing any potential cases based on these analyses.



To: John Taylor@ACRA@FDAORAHQ
Cc:
Bcc:
From: LEGGETT@cder.fda.gov
Subject: Re: Counterfeit drug working group
e: Monday, April 12, 1999 at 10:22:53 am EDT
ach:
Certify: N

FROM too long. Original FROM is
"Donald Leggett 301-827-7355 FAX 301-594-0165" <LEGGETT@cder.fda.gov>

---------------- Original Message Follows ----------------

John:

Re:
April 5, 1999 Working draft Comments

In General:

I am uncertain as to the degree of comprehensiveness intended here, but the document ,IMHO, is highly biased toward the bulk API problem. I speculate that some may lack the experience of institutional history, pre-Flavine/OCI, of drug counterfeiting which the FDA has been effective. This is not to negate the importance of this facet of the problem, but only to point out the need for balance and contributions from those who share the historical perspective.

Yes

Along the same line, am I to understand that the intent here is limited to the strategy vis a vis importation to the exclusion of the wholly domestic aspect? If this is so, then I can better appreciate the bulk API bias.

Specific:

I last commented on II Definition and I am glad to see that further comments are welcomed on this issue. If it is agreed that the document is to deal with extra-statuatory aspects, then it should be clear by first iterating the statute, then addressing this in terms of the proposed considerations of the revision. It is in some aspects more encompassing in others more restrictive. Certainly it is fair to generate a definition for the purposes of this document. For example, if this is to enjoy international application, then aspects of the WHO definition may be of increased significance.

footnote will handle

D.Drug Listing:

About a dozen years ago, I conducted an internal regulatory audit of the activities of the Drug Listing Branch. Accordingly, I agree,"anyone can obtain a drug listing" the illegality of those drugs notwithstanding. Since such activities subsequently were contracted, the dismal record of using it as an import gatekeeper continues. Thus, the use of EES to "partially deal with this shortfall" may even be optimistic - compounded with the workload and lack of sophistication in much of the import investigator domain-the agency will need to make major changes in order to hope to cope with this growing problem.

ok

H. Import Alerts:

You are very correct that APIs can (and routinely are) labeled for non-pharmaceutical use. Commonly in the lack of labeling results in the assumption that they are "supplements" or other non-pharmaceuticals.This circumvention is widely known and successful because of the aforementioned workload/sophistication problems. As with "Drug Listing" the Import Alert system is also broken to the point that major basic changes are needed, not a Band-Aid....as long as we dont attempt to lead anyone as to the limitations of the Drug Listing and Import Alert proposals ,the Band-Aids are little improvement for broken systems.

Regulatory Proposals:

The goals of these are meritorious and all of the proposals would benefit the program. I support them fully but acknowledge the passage of many will be resisted.

I am not in a position to suggest the action leads, but hope to be a part of the process based on my experience and position responsibility.

Thank you for the opportunity to comment.

Don

FDA/ORA

Date: April 5, 1999

Note to: Joe Famulare, Frank Forgione, Malcolm Frazier, Fred Fricke, Stephanie Gray, Don Leggett, Bill McConagha, Dan Michels, Jack Mitchell, Bill Nychis, Marci Norton, Joe Phillips, Gary Pierce, Debbie Ralston, Arvin Shroff, Terry Vermillion, Brad Williams, Karen Wolnik

From: John Taylor

Subject: Counterfeit Drugs

Attached is the latest draft of a work plan that follows up on the efforts of the counterfeit drugs initiative working group that was convened from 1995-1998.

This latest draft includes the comments that I received on the last draft and a proposed timeframe for the implementation of the action items discussed in the document. The timelines will have to be adjusted but they provide a good reference point and they will provide the basis for my discussions with Dennis Baker and Gary Dykstra.

As I stated before, I also want to include a paragraph at the end of each section that outlines who has the lead for a specific action. Please include information regarding who has the lead for each task and send me your comments by April 23, 1999. If you have any questions, please do not hesitate to call me at 301-827-3101 (or 3320). Thank you.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administrat
Office of Regulatory Affairs
5600 Fishers Lane, HFC-1
Rockville, MD 20857

COUNTERFEIT DRUGS

I. Background

This document contains a work plan that follows up on the efforts of the counterfeit drugs initiative working group that was convened from 1995 to 1998. This work plan focuses on actions that can be taken by the agency to prevent and contain any public health problems associated with the importation of counterfeit drugs and their introduction into interstate commerce. These steps will help us assess how widespread the counterfeit drug problem is and help us determine whether additional steps need to be taken to refine our regulatory strategy as it relates to policing the importation of counterfeit drugs.

As much as 80 percent of the bulk pharmaceuticals used by U.S. manufacturers to produce prescription drugs is imported. In addition, the number of finished drug products manufactured abroad for the U.S. market is increasing. The Food and Drug Administration (FDA) is responsible for the safety and quality of domestic and imported pharmaceutical products under the Federal Food, Drug, and Cosmetic Act (the Act). Specifically, FDA's Center for Drug Evaluation and Research (CDER) establishes standards for the safety, effectiveness, and manufacture of prescription and over-the-counter drugs. CDER reviews the clinical tests and the manufacture of new drugs before they can be approved for the U.S. market, and it regulates the manufacture of drugs already being sold to ensure that they comply with federal statutes and regulations, including current good manufacturing practice (GMP) requirements. In addition, FDA enforces the Act's prohibitions against the importation of adulterated, misbranded, and counterfeit pharmaceutical products.

FDA has developed two strategies to ensure that drug products meet the requirements of the Act. The first strategy involves evaluating the conditions under which drugs are manufactured, packed, tested, and held, through on-site inspections. The current GMP regulations, 21 C.F.R. Parts 210 and 211, provide a framework for ensuring that pharmaceutical manufacturers produce safe, pure, and high-quality pharmaceutical products. The second strategy involves monitoring the quality of drug products through post-marketing surveillance (PMS) programs. As a part of FDA's overall strategy, the agency inspects foreign manufacturers to help ensure that pharmaceutical products entering the U.S. are safe, pure, and high in quality.

FDA has utilized many approaches to evaluate the status of foreign establishments, that manufacture products for import into the United States. Limitations on resources and the ever-increasing volume of international trade in products regulated by the FDA require the agency to continually re-evaluate its approaches. The counterfeit drug initiative working group's review and recommendations will be instrumental in helping FDA make changes that will position the agency to deal with the continued growth of global trade that, on a daily basis, brings more foreign pharmaceuticals to the U.S. shores. The steps discussed in this work plan will help FDA continue to honor its mandate to ensure that U.S. consumers receive safe and effective drugs, whether they are produced here in the U.S. or overseas.

II. Definition of a Counterfeit Drug

A counterfeit pharmaceutical is a drug (either active pharmaceutical ingredient (API), intermediate or finished dosage form) which is deliberately and fraudulently mislabeled or misbranded with respect to its identity or source. Counterfeiting can apply to innovator or generic products.[Some people expressed the concern that this definition goes beyond the scope of the statutory definition. That is not its intent. This definition is supposed to be a subset of the statutory definition but I welcome comments on this issue.]

III. Regulatory Steps

Counterfeit APIs pose a real or potential health hazard because their manufacturer is often unknown. The fact that the manufacturer is unknown means that there is no product history. Therefore, the safety and efficacy of the product cannot be assured, the impurity profile is unknown and the age, the storage, the manufacturing environment, or the synthesis of the product cannot be determined. The failure to have a product history is also important because if the counterfeit product is not manufactured in accordance with GMPs this can negatively impact the quality of the finished product since no amount of finished product testing can build quality into the product. Moreover, the failure to have a product history means that research and development efforts and the clinical trials done by legitimate pharmaceutical product manufacturers are negated.

The participants in illegal counterfeiting activity may include manufacturers of bulk pharmaceuticals, manufacturers and repackers who relabel and launder bulk pharmaceuticals, importers, brokers, domestic agents, and purchasing agents either acting alone or in concert with a corporate unit. There are certain products that especially lend themselves to counterfeiting. In general, very expensive chemicals that are purchased in small quantities or less expensive chemicals that are purchased in very large quantities are particularly vulnerable to counterfeiting.

As discussed above, the agency has a broader strategy that is meant to ensure the safety and efficacy of imported drugs and this plan will not address the specific details of that broader strategy. Instead, this document focuses on additional actions that could be taken by FDA to further reduce the risk posed by counterfeit drugs.

A majority of the action items that follow target counterfeit APIs; however, several proposed action items will also aid in detecting counterfeit finished dosage forms. These potential action items include: continuing to meet with representatives from foreign governments and industry; developing a strategy for inspection of U.S. import agents and brokers, providing additional training for FDA import inspectors, increasing random sampling of imported products, targeting testing of selected bulk imported products, enhancing analytical and forensic methodology to analyze APIs, and continuing the development of, and providing access to the API databases.

A. Meetings with Representatives from Foreign Governments and Industry

It is an operational necessity to continue to establish working relationships with government health ministries and their corresponding national law enforcement agencies to ensure cooperative relationships are developed and communication is improved.

FDA will continue to meet with representatives from foreign governments and industries regarding the challenges of policing counterfeit drugs. Future steps also include a biannual (or biennial?) scientific exchange meeting with representatives from England, Germany, Canada, Australia, and the Netherlands. FDA will meet with pharmaceutical industry representatives from the innovator companies and generic drug companies so that we can impress upon them the importance of sharing information that comes into their possession regarding counterfeit pharmaceutical products. Companies that produce high demand products that tend to be counterfeited often do not elaborate on the actions they are taking to combat the problem. While such secrecy is understandable given the criminal nature of the enterprise, secrecy tends to contribute to the ignorance about the counterfeit drug problem because what companies find out for themselves tends to concern their own products, and they want to keep the information to themselves. This behavior, however, leads to duplicative investigatory efforts on the part of pharmaceutical industry and government investigators. Moreover, this secrecy makes it difficult to quantify the breadth of the counterfeit drug problem.

B. Post Market Sampling of Imported Products

As discussed above, FDA has developed two strategies to ensure that drug products meet the requirements of the Act: the first strategy is to evaluate the conditions under which drugs are manufactured, packed, tested, and held, through on-site inspections, and the second strategy is to monitor the quality of drug products through PMS programs.

A key aspect of the PMS strategy is the Drug Product Surveillance program. The program provides the agency with information about the quality of drugs marketed in this country through the sampling and analyzing of imported and domestic drug products. The volume of imports dictates that only a small fraction of the entries are examined. Therefore, FDA is not able to sample all entries of product that may not be in compliance with the Act. There is concern, however, that the current sampling strategy is not using the agency's resources effectively. Despite increased sampling and testing of foreign produced bulk pharmaceutical chemicals and finished dosage forms, very few problems have been detected. The fact that more than 80% of bulk pharmaceutical chemicals are produced in foreign countries and the heightened awareness of counterfeit drugs accentuates the concern.

Because of the low failure rate, counterfeit drugs, and the fact that more than 80% of bulk pharmaceuticals are produced in foreign countries, an assessment of the sampling strategy was conducted by FDA. This assessment has led to two changes. The sampling of APIs for analysis by the Forensic Chemistry Center to detect counterfeits under the PMS program was re-evaluated by the foreign product working group and revised in FY 1998. The revised program calls for the collection of five batches per year for each of the last 5 years (25 samples total) for each source of API at each finished dosage manufacturer. Three drugs were selected for sampling in FY 1998 and five drugs have been targeted for FY 1999.

In addition, CDER compliance program 7356.002F directs FDA investigators as part of their inspection assignment at a foreign API manufacturer to ask the manufacturer to provide to the Forensic Chemistry Center authentic samples of their APIs, labeling, certificates of analysis, container information, batch numbering information, size, and amounts of API produced and shipped to the United States. The authentic information is entered into the API database and used for comparison to suspect samples.

C. Additional Training for FDA Import Inspectors

FDA inspectors and investigators need accessible information to help them determine the authenticity of pharmaceutical products. One day of intensive training on how to conduct specific API inspections was provided to twelve investigators from Philadelphia, New Jersey, and New York, and to 20 investigators, chemists, and managers in San Juan District. This training sensitized the investigators to issues involving counterfeits, unapproved sources and poor GMP's in APIs.

FDA needs to sensitize additional inspectors and investigators to counterfeiting issues. FDA will provide additional dosage manufacturer and API training to FDA investigators starting with investigators in the Chicago and Detroit Districts and the Pacific Region.

D. Drug Listing

The Drug Registration and Listing System provides information on foreign pharmaceutical manufacturers based on the statutory requirement that they list the drug products they ship to the U.S. Drug Listing System pursuant to 21 C.F.R. Part 207 is currently used to determine the admissibility of imported pharmaceutical products. However, anyone can obtain a drug listing. The use of the system as a sole decision maker for admissibility has serious weaknesses. The system does not ensure that authentic sources or authentic material as described in new drug applications is in fact being offered for admission.

The drug listing database does not interface with the Compliance Status Information System (COMSAT) which provides the acceptable or unacceptable compliance status of foreign manufacturers based on the results of CGMP inspections. This COMSAT data is shared with other federal and state agencies and foreign inspectorates to ensure that pharmaceutical products purchased or cleared for import in their countries meet acceptable standards. Ideally this data should be readily available to the FDA import inspector making the admissibility decision. Because the COMSTAT system does not include the drug listing identification number FDA assigns to each manufacturer, we cannot easily match foreign manufacturers who have "listed" with their compliance status. The Drug Listing database also does not interface with OASIS to assist import officers by automatically comparing manufacturers and pharmaceutical products "listed" to products offered for importation.

To partially deal with this shortfall in the present clearance system, a pilot was initiated in Philadelphia District to provide the import inspectors access to additional databases. Using CDER's EES system increases the probability of confirming authentic sourcing of APIs. The pilot was set up in cooperation with CDER who donated a stand alone computer to provide the import inspector access to the EES and IND databases, and other inspection databases. The system allows inspectors to retrieve additional important data in about 3 to 4 minutes on any API entry. The Philadelphia District Office is a relatively small API importing area compared to New York and Los Angeles. Nonetheless, this saves Philadelphia District from making about 50 phone calls per month to CDER to verify information on these API entries. For example, the EES system allows the import inspector to determine which manufacturer is the authentic source, whether there is an approved NDA or if there is a valid IND. Also, the system provides summary inspectional data which indicates some level of CGMP coverage.

ORA should expand the pilot, giving EES access to import inspectors nationally. First priority for setting up this system will be those Districts with large API importations. Eventually all ports in the U.S. should be included. This system will increase assurances regarding the authenticity of API sources; however, cannot provide 100% assurance.

E. Enhancing Analytical and Forensic Methodology to Analyze (APIs):

It has been observed that counterfeiters are becoming more sophisticated with respect to counterfeiting labeling, containers, seals, and documents. Therefore, to detect counterfeit APIs it will be necessary to conduct forensic analysis of the API. The FCC will continue to improve its ability to detect counterfeit APIs by enhancing its expertise, forensic methodologies, and instrumentation. Numerous APIs have been collected and chemically fingerprinted. Recently, based in part on these analyses [what were the preliminary findings?], special targeted inspections were conducted in China, which resulted in one firm being placed on import alert and warning letters issued to two others.

F. Develop a Strategy for Inspection of U.S. Import Agents/Brokers

A team of two to three investigators from the Central Region and Forensic Chemistry Center will conduct inspections at selected U.S. import agents. Experience gained from these inspections will form the basis for the development of a strategy for a comprehensive evaluation of U.S. import agents.

G. Targeted Collection and Testing of Selected Imported APIs

Targeted collection and testing of APIs will be conducted. The targeting of the APIs will be based on intelligence from several sources such as:

1. Observations during inspections of domestic finished dosage manufacturers and foreign API and finished dosage manufacturers.
    a. Rejected APIs.
    b. Discrepancies in labeling, containers, certificates of analysis, container seals, sourcing documents.
    c. Discrepancies in laboratory results.
2. Information obtained during inspections of U.S. agents/brokers.
3. Selected API inspections of finished dosage manufacturers with a history of FDA violations.
4. Adverse events.
5. OCI.
6. The pharmaceutical industry.

H. Import Alerts

As discussed above, the sheer volume of imported products precludes the agency from physically examining each entry, including those entries where historical data suggests products are likely to be violative. Therefore, one approach that the agency uses to control the entry of such products is the issuance of import alerts after violative samples are found. Import alerts disseminate information to interested parties regarding problems with imported products. These alerts can be used to identify problem commodities, problem shippers, or problem importers, and they provide guidance for import coverage. An alert may cover an individual manufacturer, supplier or a particular product from an entire country. As a follow up to an inspection, import alerts may also issue where it is determined that a manufacturer is in violation of GMPs. These products can be detained without physical examination or analysis because there is an appearance of a violation of the Act.

Nonetheless, because of the volume of imported drugs, devices, and foods, import alerts can be circumvented. Especially in the case of APIs which can be labeled for non-pharmaceutical use. Most importers/brokers are aware that their entries of products under an import alert will be detained until they can provide analytical evidence that the product is not in violation of the Act. While the EEPS/OASIS identifies which products are subject to these alerts based on the coding entered into the system by the broker, if the code used varies slightly, or the name of the supplier changes, or the country of origin changes, these items may be released for distribution without any examination. Importers and brokers may enter products subject to an import alert unintentionally or intentionally.

Moreover, firms do not always withhold detained product from distribution. Although the brokers are theoretically subject to forfeiture of a bond up to triple the value of the goods, the violators do not always get caught, and the damages are usually mitigated to a portion of the goods' value. Consequently, ignoring a detention notice is considered by some to be a part of the cost of doing business. There is a need to establish enhanced procedures to ensure that an import alert notice for a product or company will, in fact, prevent the violative products from reaching the U.S. consumer.

For example, a foreign firm's import alert status should be communicated to all affected firms in the U.S. Another possible solution is preparing a formal import alert Standard Operating Procedures which provides for informing users of products on import alert of the violative status of these products. This program modification would put U.S. firms on notice that use or sale of the violative foreign product would be a violation of the Act. Specifically, one or more of the following options may be considered.

1. Letter to the Customer

A customer could be informed that prior to taking possession of the product, that once the product is in domestic channels and in their control, they may be held responsible and any violative product may be subject to regulatory action. The issuance of letters to U.S. customers that provide notification of the violative status of imported products, that the domestic firm may otherwise distribute commercially, should induce domestic firms to deal with only reputable foreign establishments.

2. Letter to the Firm

As an official notification of the import alert, a letter will be issued to the firm producing the violative product/s/. The letter will list the product or products which have been placed on import alert status. In addition, the U.S. regulatory agent (when one can be identified) will be sent a copy of this letter. Commercial agents may also be provided with a copy.

3. Notification of Applicants

All applicants naming the manufacturer of an unacceptable API within their application will be identified using CDER information systems and notified via letter of the import alert status.

4. Federal Register

CDER or ORA will periodically produce a list of import alerts for publication in the Federal Register. [Is this option repetitive in light of current practice or in the alternative unduly burdensome?]

5. Freedom of Information Act

The letter to the violative firm informing them of their drug products' import alert status will be placed on display in the FOI Office.

The advantage of utilizing the notification methods discussed above is that the steps outlined will ensure that users of products on import alert are informed of the violative status of these products. Because firms who may otherwise sell or use the violative drug product are given official notice of a product's violative nature; a broader notification strategy will provide additional assurance that an unacceptable product is not marketed. In addition, a broader notification strategy will not have serious resource implications. There are only a small number of drug GMP import alerts per year and the time required to issue the additional mailings is negligible.

Additional FDA proposals relating to import alerts include: increasing resources for auditing the accuracy of the data being entered in EEPS/OASIS; and citing counterfeit products as contraband. All of these steps would strengthen the government's ability to keep entries of violative products under control and assure they do not reach domestic trade channels.

IV. Regulations (Regulatory Proposals) Several Proposals were made by the working group and can be reconsidered now:

Several regulatory proposals were made by the counterfeit drug working group and these proposals could be reconsidered in conjunction with the Office of the Chief Counsel and the Office of Legislative Affairs. They include:

amending section 304(d)(1) to permit FDA to seize and destroy a counterfeit drug at import instead of permitting re-exportation;

amending section 301(i) to make the knowing possession of a bulk counterfeit drug a potential prohibited act;

implementing the FDAMA changes to section 510 of the Act to require the registration of foreign manufacturers and to permit tracking of product shipments from the foreign manufacturer to the importer;

requiring manufacturers to report to FDA when they have information concerning an FDA approved pharmaceutical product that is counterfeit;

requiring all U.S. manufacturers and distributors to certify (subject to the criminal penalties for lying) they are fully aware of the manufacturing activities going on in those foreign plants, that all of the manufacturing activities comport with all relevant U.S. laws and FDA's regulations; and requiring all U.S. manufacturers or distributors to only use or sell products for which the manufacturers of those products are registered and listed.

VI. Evaluation

All aspects of this program will be evaluated with respect to accomplishments, strengths, and weaknesses. This evaluation will occur during January 2000. Reports will be prepared and presentations made to ORA, CDER and the Commissioner's Office in February 2000.

Page 1 of 3

CASE INITIATION/MANAGEMENT REPORT

CREATED BY: Berg
CREATE DATE: ~~04/06/98~~ 4/21/98
DATE INITIATED: ~~04/06/98~~ 4/22/98
DATE CLOSED:
CLOSING CODE:
FORFEITURE:

CASE NUMBER:

YY	OFF	TYPE	#	J	P/I
98	SDC	705	0207		

RELATED CASES: None

S/A AGENT: **FIRST NAME:** Marc **LAST NAME:** Reardon

PRIMARY GEOGRAPHIC AREA
CITY: Chula Vista **STATE:** CA

CASE TITLE: INTER PHARMA INC.

PRIMARY AGENCY: **ACRONYM:** FDA-OCI

AGENCY NAME: Office of Criminal Investigations

PRIMARY CASE TYPE: **MFCC CODE:** 705.100

MFCC DESCRIPTION: Counterfeit Drugs – CDER

ORIGIN OF CASE – AGENCY:
ACRONYM: DEA
AGENCY - FULL NAME: Drug Enforcement Administration

SECONDARY CASE TYPE:

CODE:	DESCRIPTION:
715.100	Misbranded Products - CDER

PRODUCT NAME: Various

SECONDARY LOCATION:

CITY:	STATE:	ZIP:
Tijuana		

4/22/98

PROBABLE VIOLATIONS:

TYPE	SEC.	SUB.	CITATION
Federal	21	331	FD&C Prohibited Act
Federal	18	2320	Counterfeit goods

SECONDARY AGENCY: -

ACRONYM:	NAME:
DEA	Drug Enforcement Administration
CA BOP	California State Board of Pharmacy
USCS	U.S. Customs Service

LEGAL CONTACT:

GC Marci Norton

SUMMARY OF ACTIVITY:

In 1996, DEA began identifying Tijuana, MX, pharmacies diverting significant quantities of various controlled drugs from southern California pharmaceutical wholesalers. The continuing identification results from USCS seizures of drugs from trucks headed to Tijuana from the Chula Vista, CA area, as well through seizures from pedestrians returning from Mexico. One mail order operation was also identified circa summer of 1997. Common to all the seizures is that the drugs bear labels of the H.L. MOORE CO., New Britain, CT. Predominantly bottles labeled Butalbital, a muscle relaxer, have been seized, however, analysis of the contents identified same as acetaminophen. Contact with H.L. MOORE disclosed that INTER PHARMA INC. purchased approximately 300,000 tablets of acetaminophen from H.L. MOORE, subsequently selling those tablets to FARMACO DISTRIBUIDORA of Tijuana, MX. It is believed that INTER PHARMA and FARMACO are conspiring in the southern California area to print H.L. MOORE labels for placement on bottles of controlled and prescription drugs obtained from H.L MOORE and other U.S. companies. According to the CA State Board of Pharmacy, both INTER PHARMA and FARMACO have a violative history. Another company, identified as NOVA LABS has also been identified as a potential front company for FARMACO diversion activities.
FARMACO has also been identified by SDFO as being involved in the past as a purchaser/distributor of Indian-origin pharmaceuticals, which are rebottled and relabeled in southern California for export to Mexico and sale to U.S. citizens in Tijuana pharmacies.

INVESTIGATIVE PLAN:

Interview witnesses, obtain subpoenas, execute search warrants in order to identify the extent of counterfeiting activities for prosecutive consideration.

SUSPECTS/SUBJECTS:

INTER PHARMA INC.
FARMACO DISTRIBUIDORA
NOVA LABS
H.L. MOORE CO.
Subject History Forms submitted with CIR

CASE AGENT HISTORY:

CLOSING INFO:

MISC. COMMENTS:

FIELD OFFICE APPROVAL:

DATE: 4/10/98

Forgione, Frank

From: Widup, Richard
Sent: Tuesday, January 26, 1999 6:26 PM
To: Forgione, Frank; Haynes, Stephen
Subject: "Counterfeit" Drug Matters

Gentlemen: Here are some thoughts that I have based on the meeting that transpired this afternoon:

1. Whenever they decide and whoever they decide to pick from the Import Operations branches, they absolutely need to insure they pick someone that has first hand experience with the mail order shipments that come in.

2. Concentrating our efforts on incoming APIs and finished dosage forms is appropriate. Forgetting to include those products that are salvaged (which the FDA has never addressed to my knowledge) would be a mistake. There are several products that are manufactured and then salvaged for a number of reasons that I know end up being marketed throughout the world. Interchem has sent me faxes from suspect firms that are in just that business. We should look at these guys as well, like initiating some intelligence on them and seeing if we can break something.

3. Whatever is done concerning Import Operations should also involve those person(s), businesses, etc., that are importing products for compounding. It amazes me that the FDA will grant authority to allow someone to import a drug for research purposes without any stipulations. FDA needs to identify the amount of product that any firm can import, and delineate for what period of time they can do this. Otherwise, we are allowing anyone to import anything, provided that they complete the paperwork.

4. For what it is worth, it would be nice that any definition of "counterfeit" be similar to the definition of counterfeit as stated in Title 18. It would make prosecution that much easier in the long run. This agency doesn't need to create another definition in a vacuum.

Just a few thoughts. -Rich-

Forgione, Frank

From: Widup, Richard
Sent: Tuesday, January 26, 1999 6:43 PM
To: Fabel, Douglas
Cc: Forgione, Frank; Haynes, Stephen
Subject: FW: Counterfeit Drugs?

Doug: Frank wanted me to pass this along to you, along with some information that I recently obtained. The delay in getting this message to you is mine, as it took me a while to find someone in the FDA who could explain this process to me.

The products that were received in Memphis probably came in through the air facility.Nashville was listed because they are the district that services the Memphis FedEx facility. They were unapproved new drugs that apparently did not initially contain enough import information. More than likely, the FDA contacted the broker who in turn provided some information that was acceptable , and then the products were delivered. Since this drug is under patent, there are a couple of scenarios that might explain why attempts were made to ship it here:

1). It is a drug that is being used for compounding or some other IND process.
2). It is being sent to the US in preparation for this drug coming off patent.
3) It is an attempt to market an unapproved and possibly counterfeit version of the legitimate product.

Frank asked me to pass this along to you and ask you to have someone in Nashville follow-up on this. While these acts themselves are not "hot", this issue of "counterfeiting" is. Director Vermillion and AD Forgione have spent the better part of the last two days in meetings over at Parklawn on this matter, mostly as a result of congressional interest. In particular, it would be nice to know what happened to these products. Where were they being shipped, and for what purpose? If this is a "routine" matter, how often does it occur? Has this happened more recently that the dates than we have been provided? Is anyone in the district notified about the receipt of unapproved drugs, and if so, how is that documented? Please give me a call if you have any questions. Thank you. -Rich-

-----Original Message-----
From: Forgione, Frank
Sent: Thursday, January 21, 1999 8:25 AM
To: Widup, Richard
Subject: RE: Counterfeit Drugs?

Rich - Have you received any subsequent calls from Bennett? What action, if any have we taken to detemine who ordered the products and what action was taken by FDA.

-----Original Message-----
From: **Widup, Richard**
Sent: Wednesday, December 09, 1998 10:19 AM
To: Forgione, Frank; Haynes, Stephen
Cc: Rawls, Dwight
Subject: Counterfeit Drugs?

Gentlemen: I received an interesting telephone call this morning from Mr. Ian BENNETT, an employee of Carratu, London, England. Carratu is a private investigation firm. Carratu has been retained by SmithKline Beecham (SKB) to investigate the sending of a particular drug to the U.S. that is still under patent by SKB. Mr. BENNETT stated that he had gone online to the OASIS Database and determined that there were three entries and **detentions** of the product "paroxetine" (an anti-depressant) into the U.S. within the past year and a half:
1. Arrival date 4/27/98 in Nashville, TN. Product sent from Singapore by HT Consultants Private, LTD. Product code listed at 66VBB99. Reason for detention: unknown.

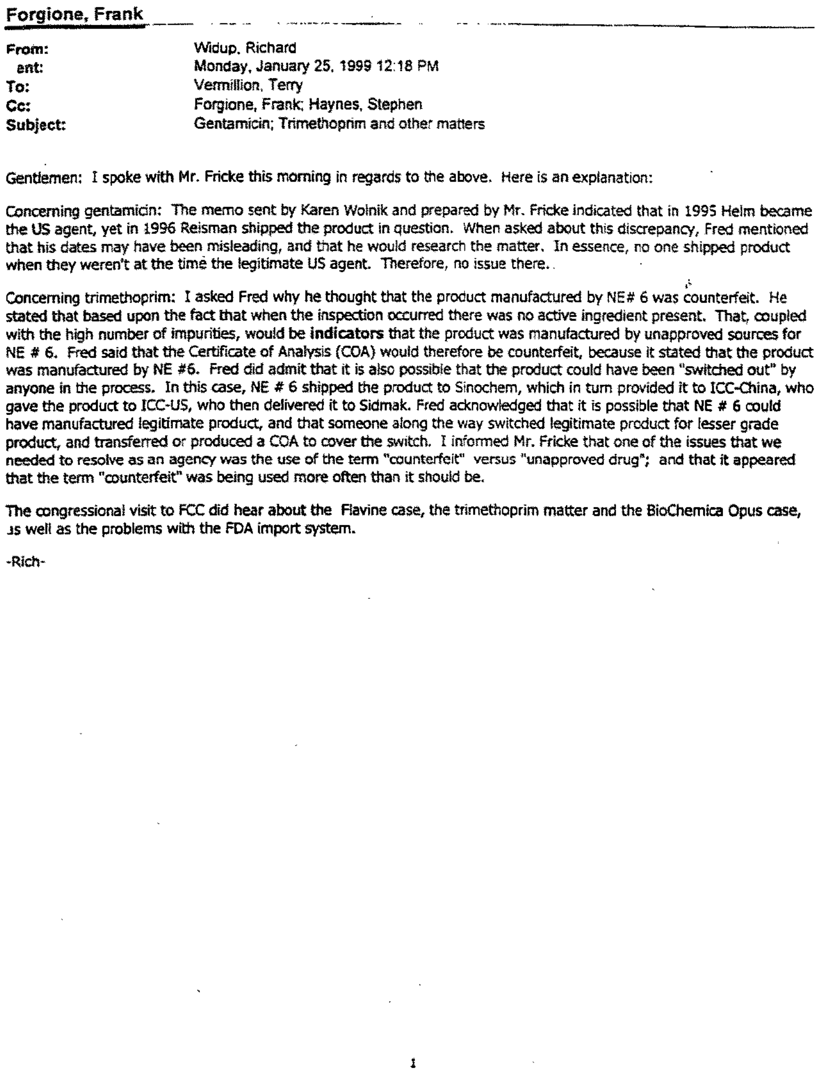
2. Arrival date 01/15/97 in Nashville, TN. Shipped from Canada (London, Canada?) by JL Ford. Reason for detention: Unapproved New Drug-No IND.

3. Arrival date 10/01/98, New York, New York. Shipped from Spain by* Medichem SA*. Reason for detention: Not Listed.

Mr. BENNETT stated that he wanted to know who these products were intended for, and if possible, the amounts shipped. He did state that * Medichem* was cleared by SKB to ship certain amounts of this product to the U.S. for research purposes ONLY.
Again, this drug is under patent and should only be manufactured by SKB or their designee.

Before I get back to him, I thought that maybe OCI ought to know this information as well. It appears that there is a breakdown in the system about alerting OCI to these potential situations. Maybe we ought to look into this to determine what the product is (was), where it is at now, how much was shipped, etc. This might be also situation where innovators are trying to send their product to the US to build up their stocks in anticipation of the product going off patent. I do not know when this occurs..but Dwight probably does if he has a current copy of the Orange Book. It could also be an outright case of marketing an Unapproved New Drug. In that case, and if the product is still around, we need to have the FDA obtain a sterile sample to send to FCC for analysis.

Please advise on how you want me to handle Mr. Bennett. Thanks. -Rich-



Forgione, Frank

From: Widup, Richard
ent: Monday, January 25, 1999 12:18 PM
To: Vermillion, Terry
Cc: Forgione, Frank; Haynes, Stephen
Subject: Gentamicin; Trimethoprim and other matters

Gentlemen: I spoke with Mr. Fricke this morning in regards to the above. Here is an explanation:

Concerning gentamicin: The memo sent by Karen Wolnik and prepared by Mr. Fricke indicated that in 1995 Helm became the US agent, yet in 1996 Reisman shipped the product in question. When asked about this discrepancy, Fred mentioned that his dates may have been misleading, and that he would research the matter. In essence, no one shipped product when they weren't at the time the legitimate US agent. Therefore, no issue there.

Concerning trimethoprim: I asked Fred why he thought that the product manufactured by NE# 6 was counterfeit. He stated that based upon the fact that when the inspection occurred there was no active ingredient present. That, coupled with the high number of impurities, would be **indicators** that the product was manufactured by unapproved sources for NE # 6. Fred said that the Certificate of Analysis (COA) would therefore be counterfeit, because it stated that the product was manufactured by NE #6. Fred did admit that it is also possible that the product could have been "switched out" by anyone in the process. In this case, NE # 6 shipped the product to Sinochem, which in turn provided it to ICC-China, who gave the product to ICC-US, who then delivered it to Sidmak. Fred acknowledged that it is possible that NE # 6 could have manufactured legitimate product, and that someone along the way switched legitimate product for lesser grade product, and transferred or produced a COA to cover the switch. I informed Mr. Fricke that one of the issues that we needed to resolve as an agency was the use of the term "counterfeit" versus "unapproved drug"; and that it appeared that the term "counterfeit" was being used more often than it should be.

The congressional visit to FCC did hear about the Flavine case, the trimethoprim matter and the BioChemica Opus case, as well as the problems with the FDA import system.

-Rich-

Forgione, Frank

From: Widup, Richard
ent: Wednesday, January 20, 1999 4:34 PM
To: Forgione, Frank
Cc: Haynes, Stephen
Subject: FW: gentamicin

Gentlemen: FYI. -Rich-

-----Original Message-----
From: kwolnik@ora.fda.gov [SMTP:kwolnik@ora.fda.gov]
Sent: Wednesday, January 20, 1999 4:05 PM
To: rwidup@oraoci.ora.fda.gov
Subject: fwd: gentamicin

Comments By: Karen Wolnik@FCC.INORGB@FDAORACER
Originally To: Karen Wolnik@FCC.INORGB@FDAORACER
Originally From: Fred Fricke@FCC.DD@FDAORACER
Original Date: 1/20/99 3:58 PM
Comments:

Rich, as you can see we drafted this email some time ago. I thought Fred sent it and I suspect he thinks he has but it was never sent. He's out of the office until Friday. Anyway, I'm sure this is what he talked to you about. If you have any questions, please give me a call.

Karen A. Wolnik, Director Inorganic Lab. Branch
USFDA Forensic Chemistry Center, 6751 Steger Dr., Cincinnati, OH 45237
Phone 513/679-2700 x181 Fax 513/679-2761
email kwolnik@ora.fda.gov

---------------------[Original Message]---------------------

Comments By: Fred Fricke@FCC.DD@FDAORACER
Originally To: Raymond Miecko@CHI.DD@FDAORACER, Jon Hunt@DEIO@FDAORAHQ, SMTP [GRAYS@CDER.FDA.GOV], Richard Widup@OCI@FDAOCIHQ
Originally Cc: Susan Setterberg@PHIRO.RFDD@FDAORACER, Joseph Phillips@PHIRO.RFDD@FDAORACER, Karen Wolnik@FCC.INORGB@FDAORACER
Originally From: Fred Fricke@FCC.DD@FDAORACER
Original Date: 1/7/99 1:56 PM
Comments:

V. Rene'e Moore, Secretary to Director, Forensic Chemistry Center
6751 Steger Drive
Cincinnati, OH 45237-3097
Phone # (513) 679-2700 ext. 184 FAX # (513) 679-2761

---------------------[Original Message]---------------------

Adverse drug events involving gentamicin sulfate injectables have been reported. The finished dosage product is produced by American Pharmaceutical Partners Inc.(APP) (formerly Fujisawa) located in Melrose Park, Illinois. The gentamicin sulfate active is manufactured by Long March Pharmaceutical Plant located in Sichuan, China. The Forensic Chemistry Center was asked to conduct analysis of these drugs in an attempt to discover the cause of the adverse drug events.

APP maintained retain samples of all the gentamicin active lots that they received from Long March starting in 1996. Samples of each of these lots were collected on November 23,1998. Numerous analyses using several different techniques were conducted on these samples but did not reveal a causative agent, however other significant and disturbing facts were discovered and are described below.

On February 9, 1996 APP/Fujisawa ordered three lots of gentamicin sulfate produced by Long March from G.M. Reisman (Long March's U.S. agent). They requested delivery by March 3,1996, and the lots were received on March 8, 1996. These lots consisted of 5Kg each and, possibly, were used for validation purposes. Also on February 9,1996, they ordered larger quantities of the same three lots to be delivered by April 3,1996. These were received on April 11, 1996, and consisted of 15 containers (5kg each) of lot # SC-GM-951108, 13 containers (5Kg. each) of lot # SC-GM-951107 and 13 containers (5Kg.each) of lot # SC-GM-951104.

A chemical "fingerprint" was established for each of the lots of gentamicin sulfate active, utilizing 2 HPLC methods, Ion Chromatography, and ICP Emission Spectrometry.

The chemical "fingerprint" for lots SC-GM-951108 and SC-GM-951107 received on March 3, 1996, is identical to the same two lots received on April 11, 1996. The chemical " fingerprint" for lot SC-GM-951104 received on March 3, 1996, is significantly different from the same lot received on April 11, 1996.

Authentic gentamicin sulfate produced by Long March was analyzed extensively in the past during the investigation of Flavine. It is interesting to note that samples of authentic material produced from 1/88 to 7/91 had a consistent chromatographic pattern (Pattern A) when analyzed by ion chromatography. Samples of material produced from 8/91 to 4/93 were consistent with one another but had a different pattern (Pattern B) than the earlier material. We do not have any more recent authentic material.

Ion chromatographic patterns were also developed for the material collected at APP/Fujisawa. With the exception of the April 11th shipment of SC-GM-951104, the material from 11/95 has Pattern A, the same pattern observed in authentics prior to 8/91. The April 11th shipment of SC-GM-951104 had Pattern B. The material manufactured from 6/96-2/98 has Pattern B. Coincidentally, after 1995 the US agent changed from Reisman to Helm.

Forgione, Frank

From: Forgione, Frank
Sent: Friday, January 29, 1999 11:10 AM
To: Vermillion, Terry
Subject: Bulk Counterfeit

Terry

I spoke with Mark Robinson, Director of Customs Fraud Investigations Division. He was very cooperative, but could provide little insight regarding the requests from the Hill regarding this subject. I mentioned some of the cases we have worked with Customs involving bulk (Flavine, FTZ). He indicated that to his knowledge any case involving bulk would be worked with OCI and that he did not believe cft bulk was a problem in the U.S. He will have his Program Manager Dan Vargas call me with any additional information they may have.

Forgione, Frank

From: Widup, Richard
ent: Saturday, February 27, 1999 4:25 PM
To: Forgione, Frank
Subject: Cross-Agency Anti-counterfeit Meeting

Frank: Tom Barker from Heatlh Canada contacted me yesterday to inform me of the details of this meeting in Ottawa in May:

The meeting will be held at the Delta Hotel in Ottawa, Canada, 361 Queen Street, Ottawa, Ontario, Canada K1R 7S9. Telephone: 800-268-1133 or 613-238-6000. Tom suggests that OCI make arrangements as soon as possible.Arrangments have been made for meeting rooms in the hotel. The hotel is centrally located and is offering rooms at $129.00, Canadian (the federal per diem rate is $91.00-which means the hotel is within our lodging rate, give or take a few dollars). Have you decided who you want to send?

I passed this information along to Bob Gillespie. He states that the Germans and the Belgians will be in attendance, along with himself. He stated that there are several people interested in attending, but that they would like an official invitation to this in order to justify the costs. I will forward the list of personnel that Bob suggested to Tom Barker.

Representatives from Malaysia would like to attend, provided that someone could pay for them. Do you believe that asset forfeiture would cover this? Might be a stretch. Anyway, this is the latest. -Rich-

FAX Transmission

FDA Central Region

Food and Drug Administration
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2nd & Chestnut Streets
Philadelphia, PA 19106

215-597-4390
215-597-5798 (fax)

Total Pages: 19

Date: 1-25-99

To: Fred Fricke
FDA/FCC

From: Deputy
Joseph X. Phillips
Regional Director

215-597-0492 (voice)

FAX: 513-679-2761

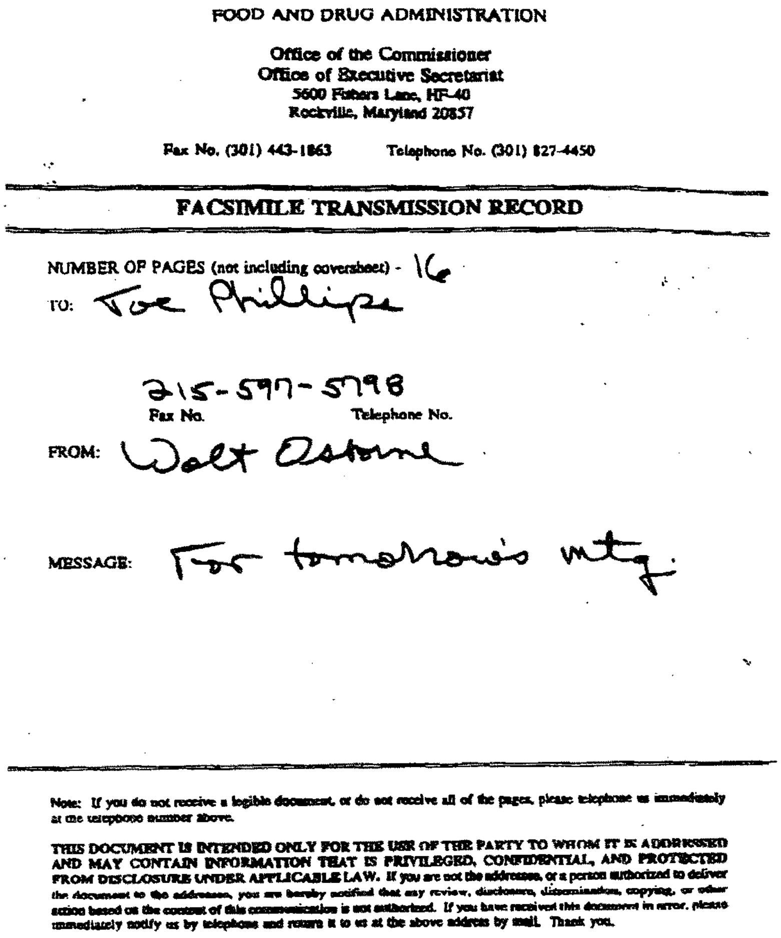
Voice:

If assistance is needed, please call 215-597-4390 x 4007

This document is intended only for the use of the addressee and may contain information that is privileged, confidential, and protected from disclosure under applicable law.

Remarks: The meeting is tomorrow 1-26-99 (not 1-27-99 as in cover letter)

Joe



FOOD AND DRUG ADMINISTRATION

Office of the Commissioner
Office of Executive Secretariat
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TO: Joe Phillips

215-597-5798
Fax No. Telephone No.

FROM: Walt Osborne

MESSAGE: For tomorrow's mtg.

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OFFICE OF THE COMMISSIONER MEETING
EXECUTIVE SUMMARY

Date: January 27, 1999
Time: 3:00-4:00 p.m.
Location: Conference Room 14-68, Parklawn

Subject: Counterfeit Drug Initiative

Attendees: Jane Henney, Michael Friedman, Randy Wykoff, Janet Woodcock, Terry Vermillion, Margaret Porter, Gary Dykstra, Joe Phillips, Fred Fricke, Jack Mitchell, Brad Williams, Walt Osborne

Meeting Purpose: to provide background report on the Counterfeit Drug Initiative and discuss and prioritize potential "next steps"

Background:

In 1995, the Cincinnati Forensic Chemistry Laboratory suggested to Dr. Kessler the possibility of establishing an agency-wide initiative related to counterfeit drugs. A number of initial meetings were held, but with varying opinions on how to address this issue, no clear-cut agenda developed. In late 1996 Dr. Kessler asked that the initiative be coordinated by the Office of Operations.

Over the subsequent year, a series of meetings was held, involving ORA management, various ORA components (including OCI, the Forensic Chemistry Lab, and ORA field staff), CDER, OSI, OCC and others. A work list of potential action items was developed, prioritized, and implemented prior to the termination of the initiative in late 1997.

The initiative was terminated for several reasons:

- While counterfeit medical products were found to be an issue of significant potential importance, no specific need for a Commissioner's Office initiative was identified.
- It was felt that the Centers and ORA were the appropriate FDA components to deal with counterfeits as a part of their on-going workload and that they should have the prerogative and responsibility to determine if proposed expenditures were justified in the face of other on-going needs.
- With the passage of FDAMA, substantial new, higher priority, responsibilities were being added to FDA.

Major actions taken by the working group included:

A) Communication

1) Outreach and Coordination was established between FDA and other foreign regulatory bodies

-Meeting with British Medicines Control Agency (April 1997 and September 1997) and with various British law enforcement groups (September 1997)
-Meeting with British, Canadian, Australian, and German regulatory authorities was held (October 1997)
-Meeting with German law enforcement authorities (January 1998)
-Meeting with Spanish National Police, Interpol, and Pharmaceutical Security Institute (November 1997)

Information about a variety of counterfeit products of concern in other countries was relayed to FDA through these meetings. Additionally, channels of communication were established or formalized.

2) Outreach and communication between FDA and industry representatives

-Meetings held with several dozen executives and senior level security managers of major domestic pharmaceutical manufacturers. Additionally, meetings were held with Pharmaceutical Security Institute (September 1997 and November 1997)

In addition to information about specific areas of concern, channels of communication were established

B) Training

1) Over 30 ORA investigators underwent specific training regarding issues related counterfeits and related issues.

C) Inspectional Activities

1) To ensure follow-up to a previous case of counterfeit bulk product, inspections were conducted at 15 finished dosage manufacturers in the United States and abroad. More than 1,000 samples were collected. Regulatory actions, including recalls, resulted from the analysis of these samples.

2) Over 50 samples of each of three commonly used bulk pharmaceutical products were collected and analyzed for impurities and chemical fingerprinting. Based in part on these analyses, special targeted inspections were conducted in China.

D) Corrective Action

1) A pilot study was initiated to permit import inspectors to have access to existing FDA databases. This pilot study, carried out in the Philadelphia District, was felt to be a success and provided import operations staff with additional valuable resources.

2) An "authentic API database" was begun by the Forensic Chemistry Laboratory.

Additional details on the actions taken by the workgroup participants are included in the attached summaries submitted by Jack Mitchell (Tab A) and Ron Chesemore (Tab B).

DISCUSSIONS AND POSSIBLE NEXT STEPS

There are several general areas where additional Agency action could be taken to further reduce the risks posed by counterfeit drugs:

1) ORA Initiative Regarding Importation of Bulk Product. ORA will develop a plan to contain any public health problems associated with the importation of counterfeit bulk products, while, at the same time, attempting to assess how widespread this problem is.

Potential action items could include.

--developing a strategy for inspection of U.S. import agents/brokers
--additional training for FDA import inspectors
--increased random sampling of imported products
--targeted testing of selected bulk imported products
--enhancing analytical and forensic methodology to analyze API's.
--evaluating the continued development of, and access to, the API Database.

2) Regulations: Several proposals were made by the working group and could be reconsidered now:

- Amend Section 304 (d)(1) to permit FDA to seize and destroy a counterfeit drug at import instead of permitting re-exportation;
- Amend section 301(l) to make the knowing possession of a bulk counterfeit drug a potential criminal act;
- Implement the FDAMA proposed changes to Section 501 of the Act to require the registration of foreign manufacturers and to permit tracking of product shipments from the foreign manufacturer to the importer;
- Require manufacturers to report to FDA when they have information concerning an FDA-approved pharmaceutical product that is counterfeit.

RELATED AREAS OF CONCERN

1) "Personal Importation" Issues. There is growing concern regarding the importation of unapproved finished pharmaceuticals both by border drive-overs and Internet orders.

2) "Compounding" issues. There is growing concern about the issues of bulk importation of unapproved products destined for compounding.

3) Foreign Trade Zones. There is growing concern about the potential of foreign trade zones to raise unique and novel challenges to FDA's regulatory authority.

4) Congressional Interest. There was substantial congressional staff interest in counterfeits during the last session. and there remains a possibility of a hearing in the early part of 1999.

Executive Secretariat Contact: Walt Osborne, 827-4431

TAB A

To: Randy Wykoff. M.D..
Associate Commissioner for Operations

Date: January 9, 1998

From: Jack Mitchell

Re: OSI Counterfeit Drug Working Group Projects

1. Pilot Program of the Establishment Evaluation System (EES) in the Philadelphia District Office Imports Branch

This pilot program, initially established in the Philadelphia District Office, was intended to test the CDER Establishment Evaluation System (EES) to determine approved sources of both finished and Active Pharmaceutical Ingredients (API). The database allows import managers timely access to additional information regarding the approval status of drugs imported into the US.

In June 1997, Ralph Lillie (CDER) and James Hunter (OSI) met with Philadelphia district office staff to review the data base assess, its strengths and weaknesses, and train staff concerning the "search" capabilities. The short training session demonstrated the time-saving features of the database. An evaluation of the trial period was planned within sixty days.

Philadelphia District Office Imports Branch Supervisor Ottavio Parenti summarized the EES trial period: Depending on the amount of information available, the period of time expended to gain access to the data ranged from forty-five seconds to two-to-four minutes. The District concluded that the data system can be learned quickly and offer easy access. It was suggested that the data system should have additional print capabilities. Some training of import entry reviewers would be required.

The District recommended EES continuation in the Philadelphia EES location, and the inclusion of one or two additional districts. EES interface with other databases (COMIS, OASIS) also must be addressed. From CDER's perspective, three issues remain: (1) to change the operating protocol from DECNet to TCP/IP (the most difficult task and CDER has not yet initiated); (2) coordination with ORA on use of two systems on one PC, and; (3) inspector training.

2. Interview Pharmaceutical Executives

Occasionally accompanied by ORA field personnel, I interviewed several pharmaceutical executives and security personnel, including former FDA'er Richard Davis, an acknowledged expert in import operations and drug inspections. We gathered background information and contacts on the severity and volume of the counterfeit drug activities, from the industry perspective, and sought cooperation in suggesting methods of preventing the problem from proliferating.

This interviewing aspect of the FDA working group was somewhat limited due to budgetary constraints and alternative priorities, and was not completed to the extent that was originally planned in latter 1996 when the working group was formed.

3. August 13, 1997, Status Report on a 1994 FDA Discussion Paper: "Recommendations to Strengthen Surveillance and Enforcement Operations With the Importation of Human Drugs", prepared by Richard Davis, then Regional Director, Mid-Atlantic Region.

Staff from ORA, CDER, and OSI met to discuss the current status of the various action items on FDA's April 20, 1995, report to the PHS Inspector General (attached). The thirteen items involve internal management decisions within ORA (headquarters, field), as well as CDER.

4. March 12, 1997 Status Report on December 1995 Report on Federal Managers' Financial Integrity Act Initiatives on Weaknesses in the Enforcement for Imported Foods - - - ORA and OSI review of updated reforms.

Although material weaknesses that were originally identified focused solely on food-related imports, the main focus of the group meeting was the possible impact of these corrective actions on FDA's enforcement program for imported bulk drug and finish dosage drug products. (Attached) This DHHS reporting procedure tracks program import program performance, and a review of the milestones has been helpful in the broader discussions.

5. People's Republic of China -- Minister of Health's list of inferior medicine and substandard manufacturing sites.

OSI obtained and then had translated with the assistance of OHA and the State Department, a People's Republic of China list of manufacturing sites which have manufactured inferior or counterfeit drug bulk products. Memo with OSI-recommended actions was circulated throughout the agency, including OHA, ORA and CDER, and OC (attached).

6. Canadian Bulk Benzocaine Drug Case: Benzocaine drums from China had entered the US on two occasions, then eventually rejected by the Canadian firm for its "off color". OSI followed up on import procedures sampling with OCI and the Buffalo District, with ultimate determination that product matched USP specifications.

7. Pharmaceutical Security Institute and the International Federation of Pharmaceutical Manufacturers Association: This industry group is composed of major multinational pharmaceutical companies. The private organization's major focus is counterfeit activities in Third World countries, particularly Southeast Asia. From this organization's perspective, counterfeit activities are "out of control", and the problems are increasing. Their FDA contacts are Stuart Nightingale and OCI.

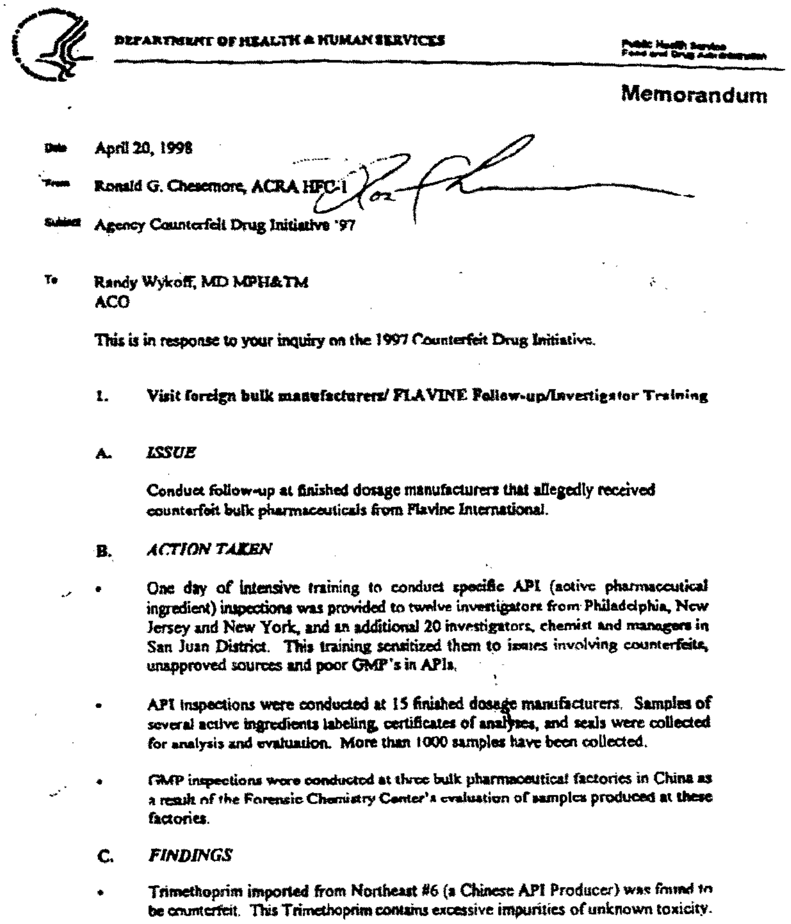
The organization offered to send information to OSI, but failed to do so, despite repeated requests.

In September, OCI (Richard Widup and Kim Rice) visited England to meet with representatives from this organization, and presumably gathered further intelligence.

Furthermore, Stephanie Grey, OCI, and others, as well as myself, met a few months ago with our British and Australian counter-parts to discuss issues of mutual interest. Although I was willing to engage in additional foreign travel to support the work of the "task force", we deferred to OCI on international visits once they became the agency's point of contact with WHO, MCA, and other outside organizations with an interest in this subject. I have no additional knowledge of information gathered as a result of these relationships or trips, other than a few mems circulated by Dr. Nightingale's office.

8. Next steps -- Most follow-up seem to fall to OCI, unless the agency decides to continue with interviews of pharmaceutical representatives and other potential sources of information, or pursue investigative leads gathered since early '97.

TAB B



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date April 20, 1998

From Ronald G. Chesemore, ACRA HFC-1

Subject Agency Counterfeit Drug Initiative '97

To Randy Wykoff, MD MPH&TM
ACO

This is in response to your inquiry on the 1997 Counterfeit Drug Initiative.

1. Visit foreign bulk manufacturers/ FLAVINE Follow-up/Investigator Training

A. *ISSUE*

Conduct follow-up at finished dosage manufacturers that allegedly received counterfeit bulk pharmaceuticals from Flavine International.

B. *ACTION TAKEN*

- One day of intensive training to conduct specific API (active pharmaceutical ingredient) inspections was provided to twelve investigators from Philadelphia, New Jersey and New York, and an additional 20 investigators, chemist and managers in San Juan District. This training sensitized them to issues involving counterfeits, unapproved sources and poor GMP's in APIs.
- API inspections were conducted at 15 finished dosage manufacturers. Samples of several active ingredients labeling, certificates of analyses, and seals were collected for analysis and evaluation. More than 1000 samples have been collected.
- GMP inspections were conducted at three bulk pharmaceutical factories in China as a result of the Forensic Chemistry Center's evaluation of samples produced at these factories.

C. *FINDINGS*

- Trimethoprim imported from Northeast #6 (a Chinese API Producer) was found to be counterfeit. This Trimethoprim contains excessive impurities of unknown toxicity.

330 mg. of impurities will be consumed in 14 days, the normal duration for Trimethoprim therapy. An inspection was conducted at Northeast #6 and a Warning Letter was issued. The office of Criminal Investigations has been alerted.

- Trimethoprim imported from Guangdong (a Chinese API producer) was found to contain excessive impurities. An inspection was conducted at Guangdong and they were placed on import alert as a result of the inspection.
- The chemical fingerprint of tetracycline from Tianjin (a Chinese API producer) did not match the authentic. An inspection was conducted at Tianjin and a Warning Letter issued.
- Several discrepancies have been found in labeling and certificates of analysis between those at the finished dosage manufacturer and the authentic API producer.
- Gross GMP deficiencies were observed at some of the finished dosage manufacturers and are being pursued by the Districts for regulatory consideration
- In cooperation with review chemists and compliance staff from CDER, the Forensic Chemistry Center conducted inspections of Biochimica and Archimica, two API manufacturers in Italy, and analyzed more than 100 samples of cefaclor intermediates and finished cefaclor. As a result of these inspections and analyses, it was proven that Biochimica and Archimica falsified their drug master files. This led to placing Biochimica in the Application Integrity program and the recall of cefaclor, minocycline, and clendamycin, both the API's from these manufacturers and the finished dosage forms made from them.
- One of the API inspection at Steris, a finished dosage manufacturer, revealed that they had used numerous unapproved sources of API's in their finished dose products. The district is considering regulatory action on this issue and poor GMP's.
- On e of the API inspections at TEVA, a finished dosage manufacturer. revealed that they were using Clindmycin from a new source, Chongqing, located in China. They produced and distributed the finished dosage product without validation of the new source. This product has been recalled.

D. NEXT STEPS

- The Forensic Chemistry Center will continue to evaluate the samples, labeling, certificates of analysis, etc. collected at the finished dosage manufacturers.
- The Forensic Chemistry Center will continue to establish and maintain an authentic API database.
- A strategy will be developed for inspection of selected U.S. Agents for API's.

Training will be provided to investigators and inspections will be conducted.

- Inspection of additional identified finished dosage manufacturers and API training for Chicago/Detroit and Pacific Region investigators.

2. **Foreign interactions with government and other officials in Europe.**

A. *ISSUE*

- Establish liaison contacts with a cross section of officials from Europe in order to open a communications channel for future cooperation to dialog on counterfeit pharmaceuticals and other FDA/OCI concerns.

B. *ACTION TAKEN*

- In October 1997 Special Agents from the Office of Criminal Investigations (OCI) headquarters, FDA/ORA's Central Region Office, and the Forensic Chemistry Center met with delegates from the Great Britain's Medicines Control Agency (MCA), Canada's Health Protection Branch (HPB), Australia's Therapeutic Goods Administration (TGA), Germany's Bundesinstitut fur Arzneimittel und Medizinprodukte (BfARM), and the National Criminal Information service. An exchange of information occurred in which the duties, functions and responsibilities of each agency were discussed and procedures for all future exchange of information were established. Additionally, these agents met with various security managers from several international pharmaceutical companies. During these meetings, the duties and functions of OCI were explained, and issues regarding the diversion, counterfeiting, misbranding and mislabeling of pharmaceutical products were discussed.

- Similar contacts were made with various government law enforcement representatives from the Federal Republic of Germany with resulted in establishing a professional working relationship between the BKA (the German Federal Police agency) and OCI. In January of 1998, this relationship was further developed during a meeting between the Director of OCI, and the Director of the BKA section that has responsibility for coordinating law enforcement investigations similar to those enforced by OCI.

- In November 1997, the OCI Director and Assistant Director for Investigations met with senior law enforcement officials from the Spanish National Police, department heads from Interpol in Lyon, France, the Acting Director of the Pharmaceutical Security Institute and international representatives attending the WHO conference in Geneva pertaining to pharmaceutical counterfeiting.

C. *FINDINGS*

- Analytical methodology, results, and other technical information were shared for numerous API's.
- Information and methodology was shared on glycerin and diethylene-glycol related to Haiti.
- Omeprazole distributed in the United Kingdom was identified as counterfeit by the MCA.
- Counterfeit meperidine was identified by Germany's Federal institute for Drugs (BFARM). Several people in Belgium suffered irreversible Parkinson's disease-like symptoms after taking only one dose. This was due to a trace impurity in the counterfeit bulk pothidine.
- Counterfeit bulk sulfamethoxazole was identified by the Therapeutic Goods Administration (TGA) in Australia.
- Counterfeit nalbuphine was identified by the British medicines Control Agency (MCA) and analyzed by the Forensic Chemistry Center. The finished dosage product was labeled as Dupont Merck.
- Methodology to detect impurities in Trimethoprim was presented by the representative from BfARM.
- Herbal products were discussed and the TGA representative reported on finding aristolochic acid (a potent carcinogen) in stephania tetrandria (a Chinese herbal product). The BfARM representative reported on cadmium in St. John's Wort.
- A "Hammer" award was presented to the Mid-Atlanta Regional Office, the Forensic Chemistry Center and the British Medicines Control Agency for cooperation and sharing of analytical and forensic methodology and associated intelligence on active pharmaceutical ingredients.
- In general all of the individual that were contacted were concerned about the manufacture and distribution of counterfeit pharmaceuticals in their countries. Most of their concerns were in the area of finished pharmaceuticals although they were aware of the possibilities of the danger posed by API counterfeiting. During these meetings FDA's concerns were explained and OCI's responsibilities and capabilities were described. Discussions were held regarding the most productive ways to enhance cooperation by both exchanging information and providing assistance during future investigations.

D. *NEXT STEPS*

- A biannual meeting will be held with the MCA, TGA, BfARM, HPB and CER/FCC and a parallel meeting will be held with representatives from the office of Criminal Investigations and their counterparts from England, Germany, Canada, and Australia. These meeting will continue to strengthen our international collaboration on API's as well as other areas such as toxic contaminants in herbals, and dosage form counterfeits. Estimated cost: $9,000

- A representative from Australia's TGA (Ph.D. in organic chemistry) will spend three months at the Forensic Chemistry Center. Funding has been approved by the TGA.

- It is an operational necessity to continue to establish working relationships with government health ministries and their corresponding national law enforcement agencies to assure cooperative relationships are developed and communication is improved. Furthermore, we recommend that OCI establish a foreign post in Europe to assure FDA's mission is advanced effectively.

3. **Meet with pharmaceutical industry.**

A. *ISSUE*

- Meet with top level executives in pharmaceutical industry to encourage sharing of intelligence on potential counterfeit and unapproved sourcing information.

B. *ACTION TAKEN*

- Meetings were held with vice-presidents of Eli Lilly and Dupont Merck.

C. *FINDINGS*

- Eli Lilly representatives shared information on a potential falsification of drug master files by Archimica and Biochimica regarding cefaclor. This led to investigations which resulted in placing Biochimica under the Application Integrity Policy and massive recalls of cefaclor, minocyline, and clendaymcin in bulk and finished dosage forms.

- Dupont Merck representatives shared information regarding counterfeiting of nalbuphine (Nubain injection) in the United Kingdom. This information was shared with the UK's MCA who conducted investigations to get counterfeit product under control.

D. *NEXT STEP*

- Continue to be interactive with industry leaders as time and resource permits.

4. Databases/Domestic Liaison Initiatives

A. *ISSUE*

- About 70% of all active pharmaceutical chemicals are imported. The import admissibility of APIs is currently determined by checking drug listing data (21 CFR-Part 207). Anyone can obtain drug listing for their product. Drug listing does not assure authentic material or source of the API.

- Initiate contact with domestic pharmaceutical manufactures security managers to discuss counterfeit pharmaceuticals.

B. *ACTION TAKEN*

- A pilot was initiated in Philadelphia District's Import Office to give import inspectors access to additional databases which would increase the probabilities of confirming authentic searching of APIs. The pilot was set up in cooperation with CDER who donated a "stand-alone" computer to provide access to EES, IND databases and some inspection data bases. They also provided training to the import inspectors.

- Continuing liaison meeting with senior level security managers from the major domestic pharmaceutical manufactures have been established by OCI. The responsibilities, capabilities, expectations and concerns of FDA/OCI are discussed during these contacts and attempts are made to establish professional working relationships between OCI and the security departments of the regulated pharmaceutical manufactures. As a result, many cooperative relationships have been developed.

C. *FINDINGS*

- Philadelphia District is a relatively small API importing area compared to New York or Los Angeles. The pilot has been ongoing in Philadelphia for about one year. The system allows inspectors to get the additional data on any given entry in about 3 to 4 minutes. It saves the Philadelphia District from making about 50 calls per month to CDER to verify information on searching. The system was installed with CDER's cooperation and volunteered equipment at virtually no cost to ORA.

  We estimate it could be installed in additional Districts at a cost of a new stand-alone computer, some installation costs, and some small training costs.

  The pilot involves use of two computers. At this time, OASIS does not provide the additional data required.

- All of these security representatives acknowledge that a counterfeit problem may affect their companies. Most feel that although the potential exists domestically, their main problems exists in the overseas market especially in the developing countries. However, all security representatives acknowledge that counterfeits manufactured overseas could make their way into U.S. commerce. Additionally, these representatives find that their companies are reluctant to provide information to the FDA related to counterfeiting of their products as the company fears adverse publicity and the loss of revenue. Many of these security representatives want to have a close working relationship with OCI, however, they often find themselves unable to receive permission from company officials. However, some of the security representatives felt their management does not encumber their interaction with law enforcement.

D. *NEXT STEPS*

- The pilot system appears to be working well in Philadelphia. Philadelphia's API entries consist primarily of chemicals for the name brand industry. Little, if any, generic APIs are received in Philadelphia ports.

  It may be well to consider expanding the pilot program to New York District where more generic APIs are received.

  The pilot program does give increased assurances on authenticity of sources of APIs.

- It is important for OCI to continue to develop the working relationships with the domestic pharmaceutical security departments and to be in a position to respond to their referrals effectively. Continued liaison at the OCI headquarters and field level is necessary. However, cooperation could be greatly improved through promulgation of a regulation requiring FDA regulated pharmaceutical manufacturers to report suspected or actual counterfeiting of their pharmaceuticals (approved by the Agency) to FDA without delay.

5. Mail Imports

A. *ISSUE*

- Is there a risk for the introduction of counterfeit pharmaceuticals to the US posed by mail imports?

B. *ACTION TAKEN*

- Mail imports cover official and commercial letters and parcels sent into the U.S. The U.S. Customs Service and Postal Service receive these items in designated handling locations. The entry is considered as a foreign entry and therefore subject to USCS regulations regarding declaration. Millions of items are received each day and they are screened in many different ways. Initial screening is performed by the USCS and Postal Service and items that may be of interest to FDA are segregated for further examination by FDA inspectors. Items that are legal for U.S. entries are passed on to the mail import situation.

C. *FINDINGS*

- At present, ti is premature to make informed conclusions relative to the exposure presented in the areas of mail imports. It is a safe assumption to say that the mail imports are highly vulnerable to misuse and present a vulnerable method for illegal products to enter the U.S., including counterfeits. It is also noteworthy that only a small fraction of the daily entries may be screened and the methods for screening vary. As a result OCI is concerned that the potential exists for harmful products to enter the U.S. undetected and these products could end up for sale in the marketplace.

D. *NEXT STEPS*

- at the conclusion of the ongoing mail project, data will be analyzed and the mail vulnerability issue will be reviewed. The misuse and misinterpretation of the FDA Personal Importation Policy complicate the issue pertaining to the receipt of mail packages containing pharmaceuticals. It is also evident that the Agency must take corrective steps to assure that other government agencies that have legal authority to oversee imports are fully instructed on the legitimate use of the Personal Importation Policy. Additionally the FDA will need to be prepared to respond to the increased enforcement by these agencies in a consistent and timely manner.

FDA/ORA

Date: April 5, 1999

Note to: Joe Famulare, Frank Forgione, Malcolm Frazier, Fred Fricke, Stephanie Gray, Don Leggett, Bill McConagha, Dan Michels, Jack Mitchell, Bill Nychis, Marci Norton, Joe Phillips, Gary Pierce, Debbie Ralston, Arvin Shroff, Terry Vermillion, Brad Williams, Karen Wolnik

From: John Taylor

Subject: Counterfeit Drugs

Attached is the latest draft of a work plan that follows up on the efforts of the counterfeit drugs initiative working group that was convened from 1995-1998.

This latest draft includes the comments that I received on the last draft and a proposed timeframe for the implementation of the action items discussed in the document. The timelines will have to be adjusted but they provide a good reference point and they will provide the basis for my discussions with Dennis Baker and Gary Dykstra.

As I stated before, I also want to include a paragraph at the end of each section that outlines who has the lead for a specific action. Please include information regarding who has the lead for each task and send me your comments by April 23, 1999. If you have any questions, please do not hesitate to call me at 301-827-3101 (or 3320). Thank you.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of Regulatory Affairs
5600 Fishers Lane, HFC-1
Rockville, MD 20857

COUNTERFEIT DRUGS

I. Background

This document contains a work plan that follows up on the efforts of the counterfeit drugs initiative working group that was convened from 1995 to 1998. This work plan focuses on actions that can be taken by the agency to prevent and contain any public health problems associated with the importation of counterfeit drugs and their introduction into interstate commerce. These steps will help us assess how widespread the counterfeit drug problem is and help us determine whether additional steps need to be taken to refine our regulatory strategy as it relates to policing the importation of counterfeit drugs.

As much as 80 percent of the bulk pharmaceuticals used by U.S. manufacturers to produce prescription drugs is imported. In addition, the number of finished drug products manufactured abroad for the U.S. market is increasing. The Food and Drug Administration (FDA) is responsible for the safety and quality of domestic and imported pharmaceutical products under the Federal Food, Drug, and Cosmetic Act (the Act). Specifically, FDA's Center for Drug Evaluation and Research (CDER) establishes standards for the safety, effectiveness, and manufacture of prescription and over-the-counter drugs. CDER reviews the clinical tests and the manufacture of new drugs before they can be approved for the U.S. market, and it regulates the manufacture of drugs already being sold to ensure that they comply with federal statutes and regulations, including current good manufacturing practice (GMP) requirements. In addition, FDA enforces the Act's prohibitions against the importation of adulterated, misbranded, and counterfeit pharmaceutical products.

FDA has developed two strategies to ensure that drug products meet the requirements of the Act. The first strategy involves evaluating the conditions under which drugs are manufactured, packed, tested, and held, through on-site inspections. The current GMP regulations, 21 C.F.R. Parts 210 and 211, provide a framework for ensuring that pharmaceutical manufacturers produce safe, pure, and high-quality pharmaceutical products. The second strategy involves monitoring the quality of drug products through post-marketing surveillance (PMS) programs. As a part of FDA's overall strategy, the agency inspects foreign manufacturers to help ensure that pharmaceutical products entering the U.S. are safe, pure, and high in quality.

FDA has utilized many approaches to evaluate the status of foreign establishments, that manufacture products for import into the United States. Limitations on resources and the ever-increasing volume of international trade in products regulated by the FDA require the agency to continually re-evaluate its approaches. The counterfeit drug initiative working group's review and recommendations will be instrumental in helping FDA make changes that will position the agency to deal with the continued growth of global trade that, on a daily basis, brings more foreign pharmaceuticals to the U.S. shores. The steps discussed in this work plan will help FDA continue to honor its mandate to ensure that U.S. consumers receive safe and effective drugs, whether they are produced here in the U.S. or overseas.

II. Definition of a Counterfeit Drug

A counterfeit pharmaceutical is a drug (either active pharmaceutical ingredient (API), intermediate or finished dosage form) which is deliberately and fraudulently mislabeled or misbranded with respect to its identity or source. Counterfeiting can apply to innovator or generic products.[Some people expressed the concern that this definition goes beyond the scope of the statutory definition. That is not its intent. This definition is supposed to be a subset of the statutory definition but I welcome comments on this issue.]

III. Regulatory Steps

Counterfeit APIs pose a real or potential health hazard because their manufacturer is often unknown. The fact that the manufacturer is unknown means that there is no product history. Therefore, the safety and efficacy of the product cannot be assured, the impurity profile is unknown and the age, the storage, the manufacturing environment, or the synthesis of the product cannot be determined. The failure to have a product history is also important because if the counterfeit product is not manufactured in accordance with GMPs this can negatively impact the quality of the finished product since no amount of finished product testing can build quality into the product. Moreover, the failure to have a product history means that research and development efforts and the clinical trials done by legitimate pharmaceutical product manufacturers are negated.

The participants in illegal counterfeiting activity may include manufacturers of bulk pharmaceuticals, manufacturers and repackers who relabel and launder bulk pharmaceuticals, importers, brokers, domestic agents, and purchasing agents either acting alone or in concert with a corporate unit. There are certain products that especially lend themselves to counterfeiting. In general, very expensive chemicals that are purchased in small quantities or less expensive chemicals that are purchased in very large quantities are particularly vulnerable to counterfeiting.

As discussed above, the agency has a broader strategy that is meant to ensure the safety and efficacy of imported drugs and this plan will not address the specific details of that broader strategy. Instead, this document focuses on additional actions that could be taken by FDA to further reduce the risk posed by counterfeit drugs.

A majority of the action items that follow target counterfeit APIs; however, several proposed action items will also aid in detecting counterfeit finished dosage forms. These potential action items include: continuing to meet with representatives from foreign governments and industry; developing a strategy for inspection of U.S. import agents and brokers, providing additional training for FDA import inspectors, increasing random sampling of imported products, targeting testing of selected bulk imported products, enhancing analytical and forensic methodology to analyze APIs, and continuing the development of, and providing access to the API databases.

A. Meetings with Representatives from Foreign Governments and Industry

It is an operational necessity to continue to establish working relationships with government health ministries and their corresponding national law enforcement agencies to ensure cooperative relationships are developed and communication is improved.

FDA will continue to meet with representatives from foreign governments and industries regarding the challenges of policing counterfeit drugs. Future steps also include a biannual (or biennial?) scientific exchange meeting with representatives from England, Germany, Canada, Australia, and the Netherlands. FDA will meet with pharmaceutical industry representatives from the innovator companies and generic drug companies so that we can impress upon them the importance of sharing information that comes into their possession regarding counterfeit pharmaceutical products. Companies that produce high demand products that tend to be counterfeited often do not elaborate on the actions they are taking to combat the problem. While such secrecy is understandable given the criminal nature of the enterprise, secrecy tends to contribute to the ignorance about the counterfeit drug problem because what companies find out for themselves tends to concern their own products, and they want to keep the information to themselves. This behavior, however, leads to duplicative investigatory efforts on the part of pharmaceutical industry and government investigators. Moreover, this secrecy makes it difficult to quantify the breadth of the counterfeit drug problem.

B. Post Market Sampling of Imported Products

As discussed above, FDA has developed two strategies to ensure that drug products meet the requirements of the Act: the first strategy is to evaluate the conditions under which drugs are manufactured, packed, tested, and held, through on-site inspections, and the second strategy is to monitor the quality of drug products through PMS programs.

A key aspect of the PMS strategy is the Drug Product Surveillance program. The program provides the agency with information about the quality of drugs marketed in this country through the sampling and analyzing of imported and domestic drug products. The volume of imports dictates that only a small fraction of the entries are examined. Therefore, FDA is not able to sample all entries of product that may not be in compliance with the Act. There is concern, however, that the current sampling strategy is not using the agency's resources effectively. Despite increased sampling and testing of foreign produced bulk pharmaceutical chemicals and finished dosage forms, very few problems have been detected. The fact that more than 80% of bulk pharmaceutical chemicals are produced in foreign countries and the heightened awareness of counterfeit drugs accentuates the concern.

Because of the low failure rate, counterfeit drugs, and the fact that more than 80% of bulk pharmaceuticals are produced in foreign countries, an assessment of the sampling strategy was conducted by FDA. This assessment has led to two changes. The sampling of APIs for analysis by the Forensic Chemistry Center to detect counterfeits under the PMS program was re-evaluated by the foreign product working group and revised in FY 1998. The revised program calls for the collection of five batches per year for each of the last 5 years (25 samples total) for each source of API at each finished dosage manufacturer. Three drugs were selected for sampling in FY 1998 and five drugs have been targeted for FY 1999.

In addition, CDER compliance program 7356.002F directs FDA investigators as part of their inspection assignment at a foreign API manufacturer to ask the manufacturer to provide to the Forensic Chemistry Center authentic samples of their APIs, labeling, certificates of analysis, container information, batch numbering information, size, and amounts of API produced and shipped to the United States. The authentic information is entered into the API database and used for comparison to suspect samples.

C. Additional Training for FDA Import Inspectors

FDA inspectors and investigators need accessible information to help them determine the authenticity of pharmaceutical products. One day of intensive training on how to conduct specific API inspections was provided to twelve investigators from Philadelphia, New Jersey, and New York, and to 20 investigators, chemists, and managers in San Juan District. This training sensitized the investigators to issues involving counterfeits, unapproved sources and poor GMP's in APIs.

FDA needs to sensitize additional inspectors and investigators to counterfeiting issues. FDA will provide additional dosage manufacturer and API training to FDA investigators starting with investigators in the Chicago and Detroit Districts and the Pacific Region.

D. Drug Listing

The Drug Registration and Listing System provides information on foreign pharmaceutical manufacturers based on the statutory requirement that they list the drug products they ship to the U.S. Drug Listing System pursuant to 21 C.F.R. Part 207 is currently used to determine the admissibility of imported pharmaceutical products. However, anyone can obtain a drug listing. The use of the system as a sole decision maker for admissibility has serious weaknesses. The system does not ensure that authentic sources or authentic material as described in new drug applications is in fact being offered for admission.

The drug listing database does not interface with the Compliance Status Information System (COMSAT) which provides the acceptable or unacceptable compliance status of foreign manufacturers based on the results of CGMP inspections. This COMSAT data is shared with other federal and state agencies and foreign inspectorates to ensure that pharmaceutical products purchased or cleared for import in their countries meet acceptable standards. Ideally this data should be readily available to the FDA import inspector making the admissibility decision. Because the COMSTAT system does not include the drug listing identification number FDA assigns to each manufacturer, we cannot easily match foreign manufacturers who have "listed" with their compliance status. The Drug Listing database also does not interface with OASIS to assist import officers by automatically comparing manufacturers and pharmaceutical products "listed" to products offered for importation.

To partially deal with this shortfall in the present clearance system, a pilot was initiated in Philadelphia District to provide the import inspectors access to additional databases. Using CDER's EES system increases the probability of confirming authentic sourcing of APIs. The pilot was set up in cooperation with CDER who donated a stand alone computer to provide the import inspector access to the EES and IND databases, and other inspection databases. The system allows inspectors to retrieve additional important data in about 3 to 4 minutes on any API entry. The Philadelphia District Office is a relatively small API importing area compared to New York and Los Angeles. Nonetheless, this saves Philadelphia District from making about 50 phone calls per month to CDER to verify information on these API entries. For example, the EES system allows the import inspector to determine which manufacturer is the authentic source, whether there is an approved NDA or if there is a valid IND. Also, the system provides summary inspectional data which indicates some level of CGMP coverage.

ORA should expand the pilot, giving EES access to import inspectors nationally. First priority for setting up this system will be those Districts with large API importations. Eventually all ports in the U.S. should be included. This system will increase assurances regarding the authenticity of API sources; however, cannot provide 100% assurance.

E. Enhancing Analytical and Forensic Methodology to Analyze (APIs):

It has been observed that counterfeiters are becoming more sophisticated with respect to counterfeiting labeling, containers, seals, and documents. Therefore, to detect counterfeit APIs it will be necessary to conduct forensic analysis of the API. The FCC will continue to improve its ability to detect counterfeit APIs by enhancing its expertise, forensic methodologies, and instrumentation. Numerous APIs have been collected and chemically fingerprinted. Recently, based in part on these analyses [what were the preliminary findings?], special targeted inspections were conducted in China, which resulted in one firm being placed on import alert and warning letters issued to two others.

F. Develop a Strategy for Inspection of U.S. Import Agents/Brokers

A team of two to three investigators from the Central Region and Forensic Chemistry Center will conduct inspections at selected U.S. import agents. Experience gained from these inspections will form the basis for the development of a strategy for a comprehensive evaluation of U.S. import agents.

G. Targeted Collection and Testing of Selected Imported APIs

Targeted collection and testing of APIs will be conducted. The targeting of the APIs will be based on intelligence from several sources such as:

1. Observations during inspections of domestic finished dosage manufacturers and foreign API and finished dosage manufacturers.
    a. Rejected APIs.
    b. Discrepancies in labeling, containers, certificates of analysis, container seals, sourcing documents.
    c. Discrepancies in laboratory results.
2. Information obtained during inspections of U.S. agents/brokers.
3. Selected API inspections of finished dosage manufacturers with a history of FDA violations.
4. Adverse events.
5. OCI.
6. The pharmaceutical industry.

H. Import Alerts

As discussed above, the sheer volume of imported products precludes the agency from physically examining each entry, including those entries where historical data suggests products are likely to be violative. Therefore, one approach that the agency uses to control the entry of such products is the issuance of import alerts after violative samples are found. Import alerts disseminate information to interested parties regarding problems with imported products. These alerts can be used to identify problem commodities, problem shippers, or problem importers, and they provide guidance for import coverage. An alert may cover an individual manufacturer, supplier or a particular product from an entire country. As a follow up to an inspection, import alerts may also issue where it is determined that a manufacturer is in violation of GMPs. These products can be detained without physical examination or analysis because there is an appearance of a violation of the Act.

Nonetheless, because of the volume of imported drugs, devices, and foods, import alerts can be circumvented. Especially in the case of APIs which can be labeled for non-pharmaceutical use. Most importers/brokers are aware that their entries of products under an import alert will be detained until they can provide analytical evidence that the product is not in violation of the Act. While the EEPS/OASIS identifies which products are subject to these alerts based on the coding entered into the system by the broker, if the code used varies slightly, or the name of the supplier changes, or the country of origin changes, these items may be released for distribution without any examination. Importers and brokers may enter products subject to an import alert unintentionally or intentionally.

Moreover, firms do not always withhold detained product from distribution. Although the brokers are theoretically subject to forfeiture of a bond up to triple the value of the goods, the violators do not always get caught, and the damages are usually mitigated to a portion of the goods' value. Consequently, ignoring a detention notice is considered by some to be a part of the cost of doing business. There is a need to establish enhanced procedures to ensure that an import alert notice for a product or company will, in fact, prevent the violative products from reaching the U.S. consumer.

For example, a foreign firm's import alert status should be communicated to all affected firms in the U.S. Another possible solution is preparing a formal import alert Standard Operating Procedures which provides for informing users of products on import alert of the violative status of these products. This program modification would put U.S. firms on notice that use or sale of the violative foreign product would be a violation of the Act. Specifically, one or more of the following options may be considered.

1. Letter to the Customer

A customer could be informed that prior to taking possession of the product, that once the product is in domestic channels and in their control, they may be held responsible and any violative product may be subject to regulatory action. The issuance of letters to U.S. customers that provide notification of the violative status of imported products, that the domestic firm may otherwise distribute commercially, should induce domestic firms to deal with only reputable foreign establishments.

2. Letter to the Firm

As an official notification of the import alert, a letter will be issued to the firm producing the violative product/s/. The letter will list the product or products which have been placed on import alert status. In addition, the U.S. regulatory agent (when one can be identified) will be sent a copy of this letter. Commercial agents may also be provided with a copy.

3. Notification of Applicants

All applicants naming the manufacturer of an unacceptable API within their application will be identified using CDER information systems and notified via letter of the import alert status.

4. Federal Register

CDER or ORA will periodically produce a list of import alerts for publication in the Federal Register. [Is this option repetitive in light of current practice or in the alternative unduly burdensome?]

5. Freedom of Information Act

The letter to the violative firm informing them of their drug products' import alert status will be placed on display in the FOI Office.

The advantage of utilizing the notification methods discussed above is that the steps outlined will ensure that users of products on import alert are informed of the violative status of these products. Because firms who may otherwise sell or use the violative drug product are given official notice of a product's violative nature; a broader notification strategy will provide additional assurance that an unacceptable product is not marketed. In addition, a broader notification strategy will not have serious resource implications. There are only a small number of drug GMP import alerts per year and the time required to issue the additional mailings is negligible.

Additional FDA proposals relating to import alerts include: increasing resources for auditing the accuracy of the data being entered in EEPS/OASIS; and citing counterfeit products as contraband. All of these steps would strengthen the government's ability to keep entries of violative products under control and assure they do not reach domestic trade channels.

IV. Regulations (Regulatory Proposals) Several Proposals were made by the working group and can be reconsidered now:

Several regulatory proposals were made by the counterfeit drug working group and these proposals could be reconsidered in conjunction with the Office of the Chief Counsel and the Office of Legislative Affairs. They include:

amending section 304(d)(1) to permit FDA to seize and destroy a counterfeit drug at import instead of permitting re-exportation;

amending section 301(i) to make the knowing possession of a bulk counterfeit drug a potential prohibited act;

implementing the FDAMA changes to section 510 of the Act to require the registration of foreign manufacturers and to permit tracking of product shipments from the foreign manufacturer to the importer;

requiring manufacturers to report to FDA when they have information concerning an FDA approved pharmaceutical product that is counterfeit;

requiring all U.S. manufacturers and distributors to certify (subject to the criminal penalties for lying) they are fully aware of the manufacturing activities going on in those foreign plants, that all of the manufacturing activities comport with all relevant U.S. laws and FDA's regulations; and requiring all U.S. manufacturers or distributors to only use or sell products for which the manufacturers of those products are registered and listed.

V. Implementation FY '99 – FY '00

[Obviously, the dates will have to be adjusted based on my discussions with Dennis Baker and Gary Dykstra but they are a good guide].

A. U.S. Agents

1. Inspection of selected U.S. Agents 3/22/99 – 4/30/99
2. Draft program for more comprehensive evaluation of U.S. Agents 5/3/99 – 6/1/99

B. Finished Dosage Manufacturers

Inspection of selected finished dosage manufacturers. 4/12/99 – 12/30/99

C. Sample Analysis

FCC analysis and evaluation of samples. 4/5/99 – 12/30/99

D. Investigator Training

Chicago, Detroit, Cincinnati dates to be determined

Los Angeles, San Francisco dates to be determined

E. Meetings with representatives from the pharmaceutical industry 4/5/99-12/30/99

F. Meetings with representatives from other countries 5/17/99 – 5/19/99

to discuss scientific procedures related to counterfeit drugs.
other dates to be determined

G. Provide import investigators access to necessary databases 7/6/99 – 12/30/99

in selected locations

H. Provide investigators access to the FCC/API database. 7/6/99 – 12/30/99

for investigators conducting inspections of drug manufacturers

*Additional one time funding needed.

VI. Evaluation

All aspects of this program will be evaluated with respect to accomplishments, strengths, and weaknesses. This evaluation will occur during January 2000. Reports will be prepared and presentations made to ORA, CDER and the Commissioner's Office in February 2000.

[illegible]

To: John Taylor@ACRA@FDAORAHQ
Cc:
Bcc:
From: LEGGETT@cder.fda.gov
Subject: Re: Counterfeit drug working group
Date: Monday, April 12, 1999 at 10:22:53 am EDT
Attach:
Certify: N

FROM too long. Original FROM is
"Donald Leggett 301-827-7355 FAX 301-594-0165" <LEGGETT@cder.fda.gov>

———————— Original Message Follows ————————

John:

Re:
April 5, 1999 Working draft Comments

In General:

I am uncertain as to the degree of comprehensiveness intended here, but the document ,IMHO, is highly biased toward the bulk API problem. I speculate that some may lack the experience of institutional history, pre-Flavine/OCI, of drug counterfeiting which the FDA has been effective. This is not to negate the importance of this facet of the problem, but only to point out the need for balance and contributions from those who share the historical perspective.

Yes

Along the same line, am I to understand that the intent here is limited to the strategy vis a vis importation to the exclusion of the wholly domestic aspect? If this is so, then I can better appreciate the bulk API bias.

Specific:

I last commented on II Definition and I am glad to see that further comments are welcomed on this issue. If it is agreed that the document is to deal with extra-statutory aspects, then it should be clear by first iterating the statute, then addressing this in terms of the proposed considerations of the revision. It is in some aspects more encompassing in others more restrictive. Certainly it is fair to generate a definition for the purposes of this document. For example, if this is to enjoy international application, then aspects of the WHO definition may be of increased significance.

footnote will handle

D.Drug Listing:

About a dozen years ago, I conducted an internal regulatory audit of the activities of the Drug Listing Branch. Accordingly, I agree,"anyone can obtain a drug listing" the illegality of those drugs notwithstanding. Since such activities subsequently were contracted, the dismal record of using it as an import gatekeeper continues. Thus, the use of EES to "partially deal with this shortfall" may even be optimistic - compounded with the workload and lack of sophistication in much of the import investigator domain-the agency will need to make major changes in order to hope to cope with this growing problem.

ok

H.Import Alerts:

You are very correct that APIs can (and routinely are) labeled for non-pharmaceutical use. Commonly in the lack of labeling results in the

assumption that they are "supplements" or other non-pharmaceuticals.This circumvention is widely known and successful because of the aforementioned workload/sophistication problems. As with "Drug Listing" the Import Alert system is also broken to the point that major basic changes are needed, not a Band-Aid....as long as we dont attempt to mislead anyone as to the limitations of the Drug Listing and Import Alert proposals ,the Band-Aids are little improvement for broken systems.

Regulatory Proposals:

The goals of these are meritorious and all of the proposals would benefit the program. I support them fully but acknowledge the passage of many will be resisted.

I am not in a position to suggest the action leads, but hope to be a part of the process based on my experience and position responsibility.

Thank you for the opportunity to comment.

Don

Challenging the counterfeiters

Ignorance, confusion and denial of the problem of counterfeit medicines have worked to the counterfeiters' advantage, but now the international pharma industry is beginning to get to grips with the issue, explains Jacky Law.

When Aurelio Rizzo was arrested in Italy last year in connection with selling counterfeit Losec, questions were inevitably raised about the security of Europe's markets. However, these concerns were largely voiced behind closed doors. No-one, least of all the authorities, wants to fuel public anxiety. And companies with products being illegally copied have a further vested interest in keeping quiet. They don't want consumers, particularly those in the so-called first world, losing confidence in their products.

But, in this case, there was someone with no reason to keep quiet. His name is Mike Retter and he is chief executive of Medihealth, the UK wholesale company that sparked off the investigation. It was his staff that noticed something odd about this particular consignment. Their suspicions were conveyed to the drug's Swedish manufacturer, Astra, and to the UK Medicines Control Agency (MCA). Once confirmed, the entire £60,000 worth of stock was forfeited. Retter got no insurance (claims can't be made for counterfeit goods), no compensation, nothing.

Some 18 months later, when Rizzo's operation was finally uncovered, it transpired that he had contacts in Ireland, Cyprus, Tunisia, Pakistan and the UK. In all, Rizzo was thought to have dealt with six British wholesalers, five of which are believed to have unwittingly fed his goods into the UK distribution chain.

Now Retter wants to know what the MCA is doing about the situation, why the Italian wholesaler they all used is still on the MCA list of approved suppliers, and what will happen to Rizzo.

In response, Norman Greenaway, chief enforcement officer at the MCA says: "We cannot talk about specific cases. But our first priority is always to stop the activity in the interests of public health, then to decide who may or may not be culpable and whether evidence can be gathered to support a prosecution. If a licence holder is involved he also stands to lose his licence."

In most industrialised countries, medicines are controlled by ensuring that all products, manufacturers and dealers are licensed and therefore obliged to conform to certain standards. Such systems rest not so much on what people stand to gain, but what they stand to lose.

"Under the Medicines Act, we can suspend licences, revoke licences or modify them," says Dr Gordon Munro, head of inspection and enforcement at the MCA. "There is also a range of criminal offences with penalties of two years in jail and limitless fines."

Manufacturers, according to Munro, are inspected at least every two years and wholesalers every four. Particularly prone to forgery are best-selling brand products, such as Viagra. These are also randomly sampled and tested in the marketplace. "Our interest is in ensuring that the patient gets a consistent and safe product," he says.

Medicines authorities throughout the western world operate on similar principles

What exactly is a counterfeit drug?

Ignorance of the extent of the counterfeiting problem is not helped by the confusion as to what a counterfeit is. The WHO defines it as a product which is deliberately and fraudulently mislabelled with respect to identity and/or source.

Dr Omar Shakoor, lecturer in pharmaceutical technology at the Robert Gordon University in Aberdeen, UK, believes that because this definition makes no mention of the standard of the drug, the terms counterfeit and substandard are now used synonymously. "From a public health perspective, there is a difference between perfectly good products circulating as counterfeit and those that are substandard," he says.

Such distinctions carry more weight in the developing world where Shakoor did his doctoral research, analysing 96 chloroquine and antibacterial samples from Nigeria and Thailand. 'On balance,' his paper concludes, 'it appears more likely that these preparations are substandard not because of fraudulent manufacturing, but as a result of bad manufacturing practice.'

The confusion over what is a true counterfeit extends far beyond this. William Grosse, quality assurance director of Eli Lilly, has identified five categories of counterfeit activity, each requiring different legislative measures.

The first is **unapproved generics**. These, he says, tend to originate in India and China and are usually sold direct to pharmacists at a substantial discount when the innovator patent is about to expire. Speaking at a Drug Information Association meeting last year, Grosse says Lilly had encountered this practice when a patient complained that the generic equivalent to its product was not as effective.

The second, **product diversion**, occurs when countries have negotiated favourable rates from pharmaceutical companies, and to similar goals. But despite good intentions and what are arguably the tightest regulations in the world, counterfeit drugs are still getting through the net. How many and, more crucially, whether this amount is growing or not depends to some extent on individual perspective. Counterfeiting is necessarily a secretive business that includes many players with very different agendas.

Both Munro and Greenaway insist, for example, that the rise in parallel imports throughout Europe in recent years is not the major cause of counterfeiting that some people within the industry, who are against the practice of parallel importing, say it is.

"On average, in each of the past five years, we have received around a dozen allegations of counterfeiting, each of which is investigated as a matter of urgency," says Greenaway. "I don't believe we are seeing an increase of activity in this area but a greater awareness in the industry and regulatory agencies."

This helps to explain why the MCA has increased its enforcement personnel sixfold over the same period. "We have learnt that to be effective, investigations have to be adequately resourced," says Greenaway.

Unfortunately, however, the Agency cannot elaborate too much on how these extra resources are spent, highlighting one of the more frustrating paradoxes of the whole counterfeiting business. While the pharmaceutical industry needs reassurance that its expensively researched and developed drugs are not being copied willy-nilly, publicity about how the regulatory agencies are tackling the problem can give counterfeiters useful intelligence about how they work.

Pharmacies are a common sight in the Mexican border town of Tijuana and attract many US tourists eager to obtain cheaper prescription medicines.

Photograph by Tony Morrison/South American Pictures

But to at least maintain level ground with the counterfeiters and develop new techniques to deal with the problem, better channels of co-operation with the industry are paramount. And this is something the Agency is concentrating on, says Greenaway.

One of these schemes won the Agency and its US counterpart, the FDA, the prestigious Hammer Award last year. In a joint project that began in 1993, the MCA and FDA developed a technology that can verify if a particular active ingredient did in fact come from the documented manufacturing site. Dr Roger Alexander, who led the MCA team, explains that when a product is licensed, it is known where the bulk

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enabling opportunists to buy at that rate but sell them in high-cost countries at a profit.

Such an operation was recently broken in France when around FF28 million (US$5.5 million) worth of illegal medicines were seized in December 1998. The medicines, which had been bound for Africa, were repackaged with social security labels and then sold by wholesalers to pharmacists, making an illegal profit of 40%.

The third category is **counterfeit labelling**. This involves either buying the product direct from the innovators and relabelling it for sale in high-cost markets or simply putting a brand name on a generic to get a higher price.

The director of a firm of private investigators who insisted on his name being withheld due to pharmaceutical client pressure, says this approach is an increasingly common way for gangsters dealing in illegal drugs to launder money: "We are looking at a number of generic companies who find that the best way to get a higher price is to put a brand name on it," he says.

The final two categories, **counterfeit active ingredients and counterfeit finished products**, are potentially the most dangerous. At the Pharmaceutical Inspections Convention Conference, held in Finland in 1997, the Pharmaceutical Security Institute (PSI) reported: "An active pharmaceutical ingredient (API) may be counterfeited in one country, passed by a circuitous route into another for formulation; from there to a third country where the product is sold. Often the finished product transits several more countries before it reaches its final destination. To add further confusion, investigation has shown that, in a number of cases, bulk pharmaceutical containers are switched to give the appearance of a given substance emanating from a European country when, in fact, it may have originated from the Far East.

Increasingly complex and hard to detect methods are being used at each stage in the manufacturing and distribution process. The Therapeutic Goods Administration in Australia told the same conference of a delivery of sulfamethoxazole that had been manufactured in India and partially substituted with sugar milled to the same particle size as the API. The substitution was placed at the bottom of every third or fourth drum in the delivery.

Perpetrators of substitution rackets have access to sophisticated packaging technology and may even co-opt legitimate employees to provide packaging information or the packaging itself. The actual substitution often takes place immediately after the consignment of API has left the premises.

John Anderson, executive secretary of the UK's Anti-Counterfeiting Group, believes that this so-called grey marketing is becoming a bigger problem than stand-alone counterfeit operations. Basically, it involves using a factory that legitimately produces goods for, say, the Brazilian market," he says. "After six weeks, however, counterfeit goods start being produced. It's the real thing [illegible] destined to be sold in that market [illegible] product is made. "We take the most highly prescribed products – not just those under patent – and 'finger-print' the factories that supply the markets we are interested in." he says, adding that Germany, the Netherlands, Australia and Canada are now also involved in the project.

But not everyone is impressed with such efforts. William Grosse, quality assurance director at Eli Lilly, produced evidence last year that as many as 8% of drugs sold in the US are products that are either diverted there from lower-cost markets or counterfeit. This was one of several factors that prompted the US government's Oversight and Investigation Sub-committee to look into the matter.

The truth is that no-one knows the scale of the problem, shrouded as it is in ignorance, confusion and denial. The figures generally used come from the World Health Organisation (WHO) which estimates that as much as 10% of all branded medicine is counterfeit with the level rising to 50-70% in some developing countries. Lost legitimate sales have been valued at US$19 billion a year.

With so much money at stake, efforts to tackle counterfeiting are being stepped up as a matter of international concern. The issue was first raised publicly in 1985 at a conference in Nairobi, which passed a recommendation exhorting the WHO and other international and non-governmental organisations to study the feasibility of setting up a clearing-house to collect data and inform governments about the nature and extent of counterfeiting.

In 1988, the World Health Assembly adopted a resolution requesting the director-general to initiate programmes to prevent and detect counterfeit and substandard medicines. And four years later, WHO and the International Federation of Pharmaceutical Manufacturers' Association (IFPMA) jointly organised the first workshop on the subject.

While secrecy is perfectly understandable, it compounds the problem of ignorance, leading to a lot of duplicated effort

Awareness about counterfeiting gradually spread but there remained little hard data until 1994 when the Japanese government provided the WHO with funds for a three-year project to set up a database of intelligence and produce a manual on how to sample the market for counterfeits, how to analyse those samples, and how to train drug inspectors.

The manual is due for publication soon and the database, bringing together reports of counterfeiting from national regulatory authorities, industry and the press, remains the only publicly available source of information. According to Dr Kazuko Kimura, who worked on the project, it has serious limitations. "We cannot say the database is an accurate list that reflects trends," she says. "Also, countries have different definitions of what is counterfeit. It may be that the product is simply substandard. Both present problems for public health but the counter measures will be very different."

Despite these weaknesses, the database reveals that between 1982 and 1997, there were 751 detected cases of counterfeiting, a quarter of which were reported from developed countries. This means there were at least 190 cases of either counterfeiting or substandard drugs reported in the developed world in those 15 years.

Many working in the field agree that this could well be the tip of the iceberg. This is in direct contrast to the findings of the first major survey into counterfeit drugs, conducted by the International Pharmaceutical Federation and the Commonwealth Pharmaceutical Association and published in 1992, described the incidence of known counterfeits in developed countries as insignificant.

It is of particular concern to pharmaceutical companies because the more counterfeiting activity there is in the US, Europe and Japan, the more they stand to lose because of the much more significant revenue stream that emanates from these countries. As Dr Arders Vorlan of Astra says: "The action we take depends on which country the counterfeits are found in. We don't bother in India or China because there are so many pirates out there selling omeprazole that it's often not worth the money to try to stop it. But in Europe we always take action." Like most companies that produce high-demand products that tend to get illegally copied, he would not elaborate on what action.

Ignorance

While such secrecy is perfectly understandable given the criminal nature of counterfeiting, it compounds the problem of ignorance because what companies find out for themselves tends to concern their own products, and they want to keep this information to themselves. This leads to a lot of duplicated effort and was one of the main reasons that the industry, under the umbrella of the IFPMA, established its own organisation to tackle the counterfeiters, in 1997.

The Pharmaceutical Security Institute (PSI) began as a reaction to mounting evidence of counterfeiting in Asia. Certain companies pooled their resources and initiated an investigation in the Philippines where around 1,360 samples were purchased from 473 drug stores. It was found that 11% of the drug stores dealt in counterfeits and 18% in illegal imports. A total of 8% of the samples were counterfeit. These results were presented to the appropriate authorities, one person was arrested, anti-counterfeiting laws were strengthened and the Ministry of Health made changes to its staff.

The success of this operation prompted Glaxo Wellcome and Bristol-Myers Squibb to provide the initial funding for a permanent presence to look after industry interests, speak on its behalf at conferences and obtain hard evidence of what is actually going on.

A PSI representative, speaking anony-

Brazil's battle begins to pay off

by Joan Forbes

One country where the serious problem of counterfeit and substandard medicines is now very much in the public eye is Brazil. Last year saw many cases of counterfeiting exposed in high-profile media coverage, and the authorities and companies have had to take action to try to combat the illegal activities.

Fraudulent medicines are thought to account for a frighteningly high proportion of Brazil's US$10 billion pharmaceutical market. Some experts believe they represent as much as 10% of sales, although estimates vary widely. Last year the health authorities put sales of counterfeits at about R$700 million (US$538 million) annually, while the industry association, Abifarma, put them at nearer R$200 million (US$154 million).

Most of the problem occurs at the distribution level, with 85% of medicines being sold to pharmacies via distributors. Counterfeits in Brazil encompass a variety of products, many of which are free samples – often out of date – which have found their way into the wrong hands, and are adulterated and/or relabelled. Many of the counterfeiters – locally dubbed the 'medicines mafia' – are said to be well financed and well organised with modern equipment and national distribution networks and much lower prices than the legitimate industry can offer.

The Brazilian pharmaceutical market is ripe for counterfeiters because of its ample size, high per capita medicine consumption, and large number of pharmacies. Also, a large proportion of ethical products are still sold without a doctor's prescription, and the authorities have lacked the resources to conduct enough inspections.

The pharmaceutical industry in Brazil, as elsewhere, has been accused by critics of sometimes keeping counterfeiting problems quiet for fear of causing anxiety among patients. Indeed, it has recognised that public awareness of the problem contributed to the fall in pharmaceutical sales in the country last year.

However, the 'outing' of the counterfeiting problem does appear to have had a positive effect in that the issue is being taken seriously and various forms of action are now being taken. There is more awareness at all levels, and the public is being given more information on the issue.

For example, legislation setting up a new national health monitoring agency to replace the under-staffed and under-resourced body responsible for pharmaceutical regulations and inspections, was approved in January.

The health authorities also issued several new pieces of legislation last year aimed at tightening up the distribution circuit and targeting medicines manufacturing, transporting and storage. It also introduced new penalties for crimes involving fraudulent medicines. Pharmaceutical companies must now notify the authorities promptly when counterfeiting is detected or suspected. Medicine packs are to contain safety seals and scratch pads with the manufacturing company's name.

With the police, the authorities have set up a special anti-counterfeiting unit which has been investigating a large number of cases. Lists of fraudulent medicines are being published in the national press, freephone numbers have been set up for patients, and consumers have been given advice on how to check whether a product is legitimate. An adverse drug reaction notification system is also being set up.

Pharmaceutical companies have also been publishing public statements, advising patients of problems. For example, December alone saw Knoll warning the public about fraudulent versions of its Vicodin and Danakan F products, Schering-Plough issuing a statement about an adulterated version of its Scaflam tablets, and Organon reassuring patients through a press statement that a batch of Ormigrein presenting discolouration had been withdrawn and presented no health risk.

•Joan Torbett is world editor on **Scrip World Pharmaceutical News** *and a consultant editor to* Scrip Magazine.

A Brazilian policeman inspects a recent haul of counterfeit medicines.
Photograph by Maria Hippenmayer/Press Association

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mously for security reasons, says that this final remit is the hardest to fulfil, given once again the nature of the activity they are dealing with. The perpetrators not only go to great lengths to conceal their operations but few people can distinguish fakes from the genuine article. "It is incredibly well concealed. Unlike counterfeit consumer goods, the patient has absolutely no idea that the medicine they are ingesting is fake. The counterfeits usually pass through legitimate trade channels so there is usually no indication to pharmacists or patients that they could be dealing in fakes. Furthermore, the actual evidence of counterfeiting disappears once the patient takes the drug."

The PSI now has 22 member companies, all paying a flat, undisclosed, fee to fund the gathering of intelligence. Essentially, it is a clearing house for information so member companies can be informed when their products are being counterfeited and dossiers can be built up for each country and region in the world.

When appropriate, proposals are drawn up in areas that might benefit from further investigation and companies are invited to take part. Companies benefit from sharing the often considerable expenses in amassing the evidence needed to get Interpol, world customs and local crime-fighting organisations involved.

But perhaps the greatest long-term benefit will be found in the country dossiers. It is hoped that these will prompt their governments to either tighten up their existing legislation or be more proactive in enforcing it. "When we have done this we will have won the war. At the moment we are just fighting battles," says the PSI.

Nevertheless, the PSI has won some impressive battles. One led to a series of raids by US customs officials in 1997 which seized US$60 million worth of counterfeit drugs from US foreign trade zones. The produce was destined for the Mexican border town of Tijuana, for sale to US tourists. "There are certain kinds of facts that send signals which suggest that an environment is right for counterfeiting activity," says the PSI spokesman.

The signals in this case were an extraordinary concentration of pharmacies in Tijuana selling prescription goods at less than half US prices. US citizens can buy up to 90 days supply of a medicine provided they have a prescription from a US doctor – although most pharmacists don't insist on seeing one.

As a result, 800 pharmacies have sprung up in the border region, most of them clustered into areas frequented by US tourists. "There is so much money to be made, it attracts unscrupulous people to the business," says Eric Hill, a San Diego-based agent with the Drug Enforcement Agency.

The common practice is for sellers to import bulk pharmaceuticals from a country like India, where they can be obtained cheaply. Once in the US free trade zones, the drugs are packaged into smaller containers with English labelling, then shipped to the pharmacies in Mexico through sales reps.

"This problem had been rumbling for years and many companies had their own investigators looking into it," says the PSI spokesman. "But it only takes one to crack it for everyone. The public needs protecting because if they ever want redress from the drug's manufacturer, they won't find them. I tried. It was impossible."

After ignorance and confusion. denial may be the biggest obstacle in the international fight against counterfeiters. Pfizer, for example, would only admit Viagra was a possible target for counterfeiters after several news reports had been faxed to its New York headquarters outlining actual cases. Then, in the briefest of statements, a spokesperson said customs authorities throughout the world had been alerted to the problem and had been given samples of the Pfizer packaging, complete with hard-to-copy holograms, to compare with any counterfeits that might come through.

Anderson says: "The industry is noticeably more reticent than other industries. They say if people know Zantac is being faked, sales will fall but it also happens with car spares and Ford tackled it head-on. They decided to make a big noise. They cut down on dealers, set up a brand security department with good people running it and the problem has gone down. This is a good example of going against what people considered to be received wisdom."

Greater openness, according to Dr Martin Ten Han, recently retired chief of WHO's Drug Safety Unit, would also mean more ready access to the PSI database. "We would then be much better placed to discuss central methodologies for tackling the problem," he says. "If we knew that Indo-China, for example, was most affected then we could concentrate our efforts there."

The PSI maintains there is no secrecy but insists that member companies also have the right to expect information to be handled with discretion. It insists that every effort is made to ensure that confidence in legitimate products is not eroded and that the reputation of the company is not damaged by irresponsible disclosures.

The way forward?

Increased commercialisation, such as direct-to-consumer advertising, and new trading routes, such as parallel importation where counterfeiters can legally break the original packaging, are both factors that are thought to be contributing to the perceived growing number of counterfeits in first world markets. "All counterfeiters are led by bulls' eye logic which means you only counterfeit something that has both strong demand and a high price," says one leading investigator who, again, refused to be named. "It is more evident in the first world now because the operations are so much more sophisticated."

And, of course, the rewards are so much greater. "Why go to so much trouble for a couple of rand when you can earn a decent pound in Europe," said the PSI about the 60.000 counterfeit diuretic tablets that were found in a South African factory in November 1998. These are believed to have been destined for the UK.

If companies do find themselves the victims of counterfeiters and have the evidence to prove it, they have various courses of action they can take. But, in the long term, the only real way forward is to gather good intelligence about how counterfeiting gangs operate, the trading routes they take and to detect their increasingly sophisticated wares.

This means sharing data not only among the companies and law enforcement agencies, as is already happening to some extent, but also among the public at large. If, as the PSI insists, the only way to win the war against counterfeit pharmaceuticals is to have better laws and better law enforcement, then public policy has to be influenced. And that means talking about the problem publicly.

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U.S. House of Representatives
Committee on Commerce
Room 2125, Rayburn House Office Building
Washington, DC 20515–6115

February 12, 1999

The Honorable Jane Henney, M.D.
Commissioner
Food and Drug Administration
Room 14-71 (HF-1)
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Henney:

On February 1, 1999, majority and minority Committee staff met with Food and Drug Administration (FDA) officials to discuss FDA's foreign drug inspection program and view FDA's import data bases. During the meetings, the Committee staff learned the following, with the caveat that there were areas of some disagreement among FDA staff, concerning FDA's surveillance of imported drug products:

1. FDA has identified approximately 50 drug manufacturers (of what the agency refers to as "substantial" medical product) in China that appear to be currently exporting to the United States products that (a) have never been inspected by the FDA during the manufacturer's exporting history, or (b) may have been inspected, but the agency has no accounting of inspection activity. Additionally, FDA believes it likely that there are a similar number of uninspected or unaccounted manufacturers in India, and possibly other countries.

2. FDA confirmed that there are a substantial number (the FDA cannot define the exact figure) of foreign drug manufacturers exporting to the United States that have not been inspected by the agency in at least seven years. Because these manufacturers have not received FDA scrutiny for many years, FDA does not know if certain management or manufacturing changes have occurred that could affect whether the firm is in compliance with FDA's Current Good Manufacturing Practices (CGMP) requirements.

3. FDA is now limited by resources to conducting about 300 foreign drug inspections per year. Of these inspections, about 200 are for pre-approval. FDA therefore has only the resources to conduct about 100 surveillance inspections pursuant to FDA's "four tier" strategy for scheduling foreign inspections. Of these 100 surveillance inspections, most

are "follow up" inspections, or inspections to reexamine seriously violative firms that have had previous non-compliance issues. This has meant that most of FDA's available resources have been used to inspect the "tier 1" and "tier 2" firms. As a result, FDA has generally lacked the resources to inspect the so-called "tier 3" and "tier 4" firms under their proposed four-tier strategy. Tiers 3 and 4 generally include *non-sterile finished* and *non-sterile bulk* drug manufacturers that ship to the United States.

4. FDA confirmed that counterfeiting of finished and bulk drug products is a growing trend in the world market. FDA believes it would be pertinent for FDA to know about an FDA-approved foreign drug manufacturer that sends counterfeit or ineffective drug products to developing countries, as this would call the integrity of the manufacturer into doubt. Nevertheless, international counterfeiting incidents are not formally monitored by FDA officials outside the Office of Criminal Investigations (OCI). To the extent that OCI obtains such information on such incidents, this information is not available to the rest of FDA.

5. Excluding excipient products, between July and December of 1998, 5,500 firms shipped pharmaceutical products (based on FDA drug product codes) to the United States . However, FDA's data bases (called COMSTAT and OCFITS) contains information on only about 20 percent, or approximately 1,100 of these firms.

6. FDA does not collect data to assess the amount of unacceptable or adulterated active pharmaceutical ingredients shipped to the U.S. from foreign sources. Further, FDA does not collect data that would allow it to track trends or catalog the quality of products coming from abroad. Finally, FDA does not require any reporting from any U.S. manufacturer if it discovers adulterated or substandard material.

7. The U.S. "broker" or "agent"of the U.S. manufacturer is often the consignee of record for shipments of imported drug products. In those cases where the shipments are to the U.S. broker or to a warehouse not belonging to the final consignee, FDA does not have a definitive or realtime capability to determine which domestic manufacturer is receiving the foreign drug product.

8. Ordinary analytical testing of bulk and finished drug products does not completely assure safety and efficacy. For example, the ordinary testing performed by U.S. manufacturers would not necessarily detect cross-contaminations from ingredients such as pesticides or penicillin, nor would ordinary testing necessarily detect counterfeit ingredients.

9. FDA has not developed a formal plan to secure a predefined number of inspectors that would allow it to meet its desired CGMP foreign drug inspection frequency of once every two years, or to meet the frequency defined by FDA's four-tiered inspection strategy.

Moreover, FDA has not formally identified the amount of inspectors required to reach that goal.

10. FDA has not conducted any formal analysis to measure the effect that failure to meet FDA's inspection frequency (*i.e.*, once every two years) has had on the quality of foreign pharmaceutical imports.

These facts and conclusions are critical to our review of FDA's foreign drug inspection program. If the FDA believes these conclusions are in error, please provide written comments by March 1, 1999. If you have any questions, please have your staff contact Mr. Alan Slobodin of the Majority staff at (202) 225-2927 or Mr. Chris Knauer of the Minority staff at (202) 226-3400.

Thank you for your assistance.

Sincerely,

FRED UPTON
CHAIRMAN
SUBCOMMITTEE ON OVERSIGHT
AND INVESTIGATIONS

RON KLINK
RANKING MEMBER
SUBCOMMITTEE ON OVERSIGHT
AND INVESTIGATIONS

CC: TOM BLILEY, CHAIRMAN
JOHN D. DINGELL, RANKING MEMBER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR - 5 1999

The Honorable Fred Upton
Chairman, Subcommittee on
Oversight and Investigations
Committee on Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

Thank you for your letter of February 12, 1999, co-signed by Representative Ron Klink, regarding a February 1, 1999 meeting between majority and minority Committee staff and Food and Drug Administration (FDA) officials. A similar letter is being sent to Mr. Klink.

Your letter summarized certain conclusions which your staff drew from the meeting, and requested that FDA provide written comments clarifying or correcting any conclusions which we believe may be in error. For ease of reference each item is restated in boldface type, followed by our comments.

1. **FDA has identified approximately 50 drug manufacturers (of what the agency refers to as "substantial" medical product) in China that appear to be currently exporting to the United States products that (a) have never been inspected by the FDA during the manufacturer's exporting history or (b) may have been inspected, but the agency has no accounting of inspection activity. Additionally, FDA believes it likely that there are a similar number of uninspected or unaccounted manufacturers in India, and possibly other countries.**

Comments: The statement accurately reflects the information we provided in the February 1 meeting. We subsequently reviewed this information and found that the approximately 50 firms referred to include about 30 in China and about 20 in India. We apologize for the error. These figures were compiled from a review of import entry data in the Agency's OASIS database and include pharmaceutical manufacturers that currently are exporting to the United States pharmaceutical products that do not appear to have been inspected by the FDA during the manufacturer's exporting history. The OASIS data covered product entries coded as pharmaceuticals during the period January through December 1997. The Agency is in the process of including these establishments in its database of establishments to be given surveillance inspection coverage as resources permit.

2. **FDA confirmed that there are a substantial number (the FDA cannot define the exact figure) of foreign drug manufacturers exporting to the United States that have not been inspected by the agency in at least seven years. Because these manufacturers have not received FDA scrutiny for many years, FDA does not know if certain management or manufacturing changes have occurred that could affect whether the firm is in compliance with FDA's Current Good Manufacturing Practices (CGMP) requirements.**

Comments: It is correct that FDA has not determined the exact number of foreign drug manufacturers currently exporting to the United States that have not been inspected in at least seven years. However, rather than saying the Agency "cannot define" this number, it would be more accurate to say that FDA *has not* defined the exact number. It is possible to construct such a list by cross-referencing OASIS import data with inspection data from the COMSTAT and OCFITS databases. To do so by hand, however, would be extremely time consuming; therefore, we anticipate accomplishing such cross-referencing electronically as OASIS and our inspections data bases are integrated with the new FACTS data base. This process already has begun, as demonstrated by the information conveyed in statement 1 above.

3. **FDA is now limited by resources to conducting about 300 foreign drug inspections per year. Of these inspections, about 200 are for pre-approval. FDA therefore has only the resources to conduct about 100 surveillance inspections pursuant to FDA's "four tier" strategy for scheduling foreign inspections. Of these 100 surveillance inspections, most are "follow up" inspections, or inspections to reexamine seriously violative firms that have had previous non-compliance issues. This has meant that most of FDA's available resources have been used to inspect the "tier 1" and "tier 2" firms. As a result, FDA has generally lacked the resources to inspect the so-called "tier 3" and "tier 4" firms under their proposed four-tier strategy. Tiers 3 and 4 generally include non-sterile finished and non-sterile bulk drug manufacturers that ship to the United States.**

Comments: The statement accurately reflects the information we provided in the February 1 meeting. We would like to add a clarification regarding the approximately 100 inspections not related to applications. Those inspections requested for FY99 were mostly "for cause" or follow-ups to reexamine seriously violative firms. In FY98 and FY97, however, most were selected from tier 2 -- sterile drug firms that had not been inspected during the previous 3 years. We also would add that most of the 200 pre-approval inspections cover firms that have not been inspected during the previous two years, and most of the resulting inspections include general GMP compliance.

4. **FDA confirmed that counterfeiting of finished and bulk drug products is a growing trend in the world market. FDA believes it would be pertinent for FDA to know about an FDA-approved foreign drug manufacturer that sends counterfeit or ineffective drug products to developing countries, as this would call the integrity of the manufacturer into doubt. Nevertheless, international counterfeiting incidents are not formally monitored by FDA officials outside the Office of Criminal Investigations (OCI). To the extent that OCI obtains such information on such incidents, this information is not available to the rest of FDA.**

Comments: It is correct that during the meeting FDA confirmed that we are aware of reports of counterfeiting of finished and active pharmaceutical ingredient products in the world market. We would like to clarify, however, that given the current state of information, it would be difficult to state definitively that counterfeiting represents a "growing trend." FDA believes it would be valuable to know about any foreign drug manufacturer that sends counterfeit or ineffective drug products to developing countries, as this would call the integrity of the manufacturer into doubt.

We do not recall a discussion of the extent to which information about counterfeit products is shared within the Agency. We would, however, like to add that the Agency learns of counterfeiting incidents in a variety of ways, including notice from the World Health Organization (WHO) to our WHO representative, reports received by FDA's Office of Criminal Investigations (OCI), and reports received by other organizations in FDA. Such information is shared within FDA as appropriate, taking into account such factors as whether the information was obtained pursuant to a criminal investigation.

5. **Excluding excipient products, between July and December of 1998, 5,500 firms shipped pharmaceutical products (based on FDA drug product codes) to the United States. However, FDA's data bases (called COMSTAT and OCFITS) contains information on only about 20 percent, or approximately 1,100 of these firms.**

Comments: As we recall, we stated that as many as 5,500 firms shipped pharmaceutical products, *including* excipient products, over-the-counter (OTC) pharmaceuticals, health supplements, and miscellaneous products (such as packaging components). As demonstrated during the February 1 meeting, pharmaceutical product codes may include such items as caffeine for use in soft drinks, and toothbrushes. In addition, firm names, particularly those translated from Chinese, may appear as multiple firms due to spelling or other errors. Therefore it would be inaccurate to conclude that FDA has information on only 20% of the firms shipping significant human drug products into the U.S. As we proceed with the integration of import and inspection data, we expect to be able to provide a more accurate estimate.

6. **FDA does not collect data to assess the amount of unacceptable or adulterated active pharmaceutical ingredients shipped to the U.S. from foreign sources. Further, FDA does not collect data that would allow it to track trends or catalog the quality of products coming from abroad. Finally, FDA does not require any reporting from any U.S. manufacturer if it discovers adulterated or substandard material.**

Comments: With respect to comprehensive data collection, the first two sentences are correct. We would like to add, however, that CDER *does* collect data from firms that are inspected, and can use (and has used) OCFITS data to track and analyze trends in types of GMP violations by product, firm, country, etc. As discussed in the February 1 meeting, a GMP inspection includes review of records related to API shipments received, including rejections and the reasons for such rejections. While such data may not be comprehensive, it can prove helpful to illuminate emerging trends. Regarding the last sentence, as we recall, the discussion centered around manufacturers having no obligation to report adulterated or substandard material, and therefore there is no systematic means for FDA to retrieve this data.

7. **The U.S. "broker" or "agent" of the U.S. manufacturer is often the consignee of record for shipments of imported**

drug products. In those cases where the shipments are to the U.S. broker or to a warehouse not belonging to the final consignee, FDA does not have a definitive or realtime capability to determine which domestic manufacturer is receiving the foreign drug product.

Comments: It is correct that the final consignee may not be apparent from documents and computer systems at time of entry. Nevertheless, if that information were needed, it is available by placing a telephone call or visit to the U.S. agent or broker. The U.S. broker, agent, or importer/distributor that supplies the U.S. finished dosage form manufacturer may be the consignee of record in the Agency's OASIS system for shipments of imported drug products. The identification of the final consignee, if needed, could be determined by tracing the product through the distribution channels by investigations at the consignee of record.

8. **Ordinary analytical testing of bulk and finished drug products does not completely assure safety and efficacy. For example, the ordinary testing performed by U.S. manufacturers would not necessarily detect cross-contamination from ingredients such as pesticides or penicillin, nor would ordinary testing necessarily detect counterfeit ingredients.**

Comments: The statement is accurate.

9. **FDA has not developed a formal plan to secure a predefined number of inspectors that would allow it to meet its desired CGMP foreign drug inspection frequency of once every two years, or to meet the frequency defined by FDA's four-tiered inspection strategy. Moreover, FDA has not formally identified the amount of inspectors required to reach that goal.**

Comments: The statement accurately reflects our discussion in the February 1 meeting. Since that time we have begun informal discussions of the level of resources which would be required to conduct GMP inspections worldwide on a two-year basis.

10. **FDA has not conducted any formal analysis to measure the effect that failure to meet FDA's inspection frequency (i.e., once every two years) has had on the quality of foreign pharmaceutical imports.**

Comments: The statement is accurate; FDA has not conducted such an analysis. We would caution, however, that such information may be difficult to quantify and may depend on other factors, such as shifting market trends in the pharmaceutical industry.

If you have any further questions about this or any other matter, please let us know.

Sincerely,

Melinda K. Plaisier
Interim Associate Commissioner
for Legislative Affairs

cc: The Honorable Thomas J. Bliley, Jr.
Chairman, Committee on Commerce

The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce

QC

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Published by F-D-C Reports, Inc. *59 YEARS*--Devoted to Specialized Health Care Information

Vol. 32, No. 6 June 1998

A SPECIALIZED MONTHLY PUBLICATION BY F-D-C REPORTS, INC.
5550 Friendship Blvd., Suite One, Chevy Chase, MD 20815-7278 – *FAX:* (301) 664-7258; *PHONE:* (800) 332-2181; *Internet:* www.fdcreports.com

THE NEWS THIS ISSUE

☐ THE U.S.-EU MUTUAL RECOGNITION AGREEMENT equivalency determination process will be as open as possible, FDA is promising. Resources are a key issue for the agency as it seeks to respond to various pressures on its foreign inspection program, including a critique from GAO and increased Congressional scrutiny. Although FDA is moving forward on the MRA as a streamlining mechanism, it is marshalling resources in the near term to address outstanding equivalency concerns such as the inspection report format, joint training and inspection activities, and GMP standards. A broadened ICH committee has met to chart the course for a harmonized API GMP guideline. For the time being, FDA is using its recently revised domestic API guide to define GMP standards as recent foreign inspection findings indicate. Foreign drug diversion and counterfeiting are a growing FDA enforcement challenge not addressed by the MRA.

TRADE/CONSUMER GROUPS SEEK "OPEN" MRA

Equivalence determinations permitting FDA to accept site inspections conducted by European pharmaceutical regulatory bodies in lieu of its own inspectional coverage will be made with full public access to the information backing the decisions.

FDA will be assessing the equivalence of the inspection programs of the European Union states during a three year "confidence building" period provided under the pharmaceutical annex of the Mutual Recognition Agreement which was formally signed at a May 18 U.S.-EU summit in London. If equivalency is established, the results of the inspections conducted by the regulatory agency of the exporting country in the EU will be accepted by FDA.

FDA management explains that public access to the information on which equivalency determinations are based will be one way in which the agency inten to ensure that the mutual recognition process is as op as possible.

FDA Compliance Office Director Stephan Gray, who was been actively involved in the MR negotiations, made clear the agency's intention at t Drug Information Association's annual meeting Boston in June. She said that the FDA plans " provide for additional opportunities to follow an comment on the implementation of the MRA, including the equivalency evaluations. "We think it very important to have an entirely open process so th people understand why decisions were made."

➤ The FDA affirmation that the process will be a open as possible responds to concerns expresse in comments on the final MRA draft, which wa published by FDA as a "proposed rule" in th *Federal Register* in April. The text of the fina draft is almost identical to the document initiale by US and EU negotiators in June 199 following two years of negotiation ("The Gol Sheet" August 1997).

For example, the consumer advocacy grou Public Citizen asserted that "mechanisms for the publi to participate in the equivalence determination process are "crucial" and a "key feature" missing in th proposed rule. "At a bare minimum," the group stated "the factual basis for a determination of equivalenc should be publicly available and clearly understood."

The Pharmaceutical Research and Manufacturers of America (PhRMA) also emphasized the "need for the U.S. and EC officials participating in the transitional and operational phases of the MRA to maintain an active dialogue with the industry sector." PhRMA offered its "continuing assistance" to the Joint Sectoral Committee working on the pharmaceutical annex "to provide the unique technical expertise of the pharmaceutical industry in support of the Committee's efforts."

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orking group would revise, modify, or even replace he selected document as it deemed appropriate.

The second option was to perform a side-by-side comparison of the five documents and to select from them the best language in each topic area.

The third option was to start with a basic concept paper that was developed by the topic rapporteurs and presented at the meeting. The paper outlined very basic concepts on API manufacturing and controls, such as validation and control of water systems.

ICH GMP & Submission Guidelines Are Different

The expert working group quickly agreed that a side-by-side comparison was not practical. The amount of resources necessary to do such work was deemed prohibitive.

At first, the group reached a consensus to select one of the five documents as a model. Deliberations on the selection of the document proved difficult, however, and extended into the second day of the meeting.

Two camps formed, one supporting FDA's draft and the other supporting the PICS document. From FDA's perspective, its draft was the better candidate of the two because of the much more extensive revision process. The agency also felt that its document was more flexible and consistent.

On the other hand, FDA recognized that there would be resistance to its use especially from the European representatives. The agency was prepared to support the PIC document since it had been closely involved with the development of the guidance. However, a few other members of the expert working group were not sympathetic to the PIC guide which was viewed as containing too much "how to" instruction.

➤ Because a consensus is required to move forward under ICH, the expert working group decided to abandon the first option and to select the third – develop a fresh document based on the initial concept paper prepared by the rapporteurs. This decision meant that the EWG would not meet its original goal of completing a draft in six months.

FDA's Gray expects that the ICH foray into the development of a GMP guidance for bulk drugs will lead to other ICH efforts in the GMP area. One problem, she noted at the DIA meeting, will be the need to interpret ICH GMP guidance differently than its marketing application submission documents.

Gray explained that industry has heard "many times" from FDA staffers, including Office o Pharmaceutical Sciences Director Roger Williams "that the ICH guidance is the ceiling" for wha individual reviewers should be requesting. She noted that these submission guidances address many areas fo which there have not been previous guidance, statutory obligations and responsibilities, nor case law.

For the GMPs, on the other hand, Gray noted "there is not only statutory responsibility, but a lot o case law...within the U.S." She emphasized that FDA has "always said that GMPs are the minimum acceptable" standard. These "philosophica differences" will have to be "taken into account when people think of an ICH process," Gray said.

FDA Issues Revised API Guidance

While ICH moves forward with the effort to harmonize API GMPs, FDA will continue to use it domestic guidance to interpret how firms are expected to apply GMPs to bulk processes.

FDA released a revised draft of the AP guidance for comment in April. Reflecting industry comments on the previous draft ("The Gold Sheet" April 1995 & May 1997), the document includes a discussion of the concept of concurrent validation and of GMP applicability to clinical trial materials.

The guidance acknowledges that concurren validation may be acceptable in situations when neithe prospective or retrospective validation can be performed. In the clinical trials section, FDA recognizes the need for flexibility in interpreting GMP standards in the context of the evolutionary nature o the clinical manufacturing process.

➤ A review of recent "untitled letters" issued b FDA to foreign API manufacturers shows tha the wording of the guidance is being used as model to help define objectionable conditions (In general, untitled letters are issued to firms i lieu of warning letters when products covered b the inspection are not yet marketed in the U.S.)

This overlap is exemplified in a December 199 letter to a Czech bulk producer, Farmak, which detai the conditions under which the firm can institute retrospective validation program.

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This overlap is exemplified in a December 1996 letter to a Czech bulk producer, Farmak, which details the conditions under which the firm can institute a retrospective validation program.

The letter states that retrospective validation can proceed "only if API processes are fully consistent over time, adequate evidence of process controls exist, and in-process and end-product data show lot-to-lot consistency."

In the guidance, FDA makes this same point. It explains further that "consistency" means that there are no significant changes affecting the API's "critical quality attributes," such as changes in raw materials, equipment, systems, facilities, or in the production process.

The guidance adds that retrospective validation should be used "only when there is a sufficient history on past API batches to demonstrate the process consistently produces acceptable products." A component of that history includes an established impurity profile. Farmak, FDA noted in the untitled letter, must pursue prospective validation because it had not established an impurity profile for its API.

➤ Process validation was a key problem area for API manufacturers in FY 1997 as it has been in previous years ("The Gold Sheet" May 1997). Of the seven untitled letters sent to foreign API manufacturers during the past year, five referenced problems with the firms' process validation procedures (see box p. 15).

In a letter to the British manufacturer Mitchell Cotts Chemicals, FDA accepts the firm's commitment to conduct concurrent validation following the modification of one step of its API synthesis. According to the new draft of the API guidance, firms can revalidate a process concurrently when a modification is made. A retrospective validation study by Mitchell Cotts showed that the manufacturing process resulted in batches with inconsistent particle size distribution, prompting the firm to make the process modification.

In these enforcement letters, FDA continues to site foreign API facilities for deficiencies in water systems, out-of-specification result investigations, cleaning and cleaning validation, stability testing programs, and written procedures. Each of these areas are addressed in detail in the API guidance.

Overseas Manufacturing Spurs Illegal Activities

FDA has been focusing significant resources on creating a more effective and efficient foreign GMP enforcement program. However, the U.S. is also facing a significant threat to the quality of its drug supply from foreign drug diversion and counterfeiting – a problem area not addressed in the MRA negotiations nor adequately accounted for in agency resource allocations.

With the dramatic shift of pharmaceutical production from the U.S. to foreign locations over the past decade, U.S. industry and consumers are being exposed to a variety of unethical practices that could have serious health consequences. As third-world countries with fewer regulatory controls become more prominent in the drug supply chain, practices such as theft and counterfeiting are becoming an increasing enforcement problem for the U.S. and the EU.

➤ A tragedy recently occured in Haiti when glycerin containing ethylene glycol poisoned 89 children.

Elaborating on the Haiti incident, Eli Lilly Quality Assurance Director William Grosse explained at the DIA meeting that the counterfeit product originated in China and was shipped through Germany. In that case, he stated, "it did not quite make it to U.S." However, he warned, "sooner or later, we are going to have a catastrophe."

Five Types Of Criminal Activity Identified By Lilly

Grosse identified five specific criminal activities that manufacturers and regulators must guard against: ▪▪ unapproved generics ▪▪ product diversion ▪▪ counterfeit labels ▪▪ counterfeit APIs, and ▪▪ counterfeit drug products.

Unapproved generics, Grosse explained, originate primarily in India and China and make their way into the U.S. over the Mexican and Canadian borders. They are usually sold directly to pharmacies at a substantial discount to the innovator product during the period when the name brand is about to turn generic. The seller of the unapproved generic will claim that the product is as safe and effective as the innovator drug, and usually will manufacture the product to resemble the name brand. The seller may also state that a marketing application for the product is pending at FDA.

➤ Lilly encountered this practice following complaints that one of the company's products was not working. "We are finding this out through our complaint system," Grosse said. "We are finding out that [the unapproved generic] is a pretty close product but it is not our product."

Product diversion, also known as "parallel importation" or "U-boat sales," is also "becoming extremely common," Grosse warned. The practice occurs when countries exploit their ability to negotiate favorable rates from pharmaceutical companies and then sell the product back to the U.S. or the EU for a profit. "We have identified five distinct rings of criminals around the world that are active in this particular arena," Grosse maintained. These groups "frequently specify English labeling as being the only thing that the local country would have faith in."

➤ Grosse explained that the regulatory and law enforcement communities "do not know how to prosecute" those who perpetrate this crime.

The "American Goods Returned Law" which makes it illegal to reimport pharmaceuticals into the U.S. unless by the manufacturer, "does not seem to be a very strong deterrent," he asserted. Product diversion is allowed within the EU, but outlawed for products re-entering the Union.

Counterfeiting Problems On The Increase

The three forms of counterfeiting identified by Grosse are becoming a significant problem for regulators and industry alike.

Counterfeit labeling, Grosse said, is "relatively new." With new computer imaging technology, innovator labels are "extremely easy to reproduce," he explained. Criminal outfits can purchase product from innovators and relabel them for resale in the U.S. A serious concern resulting from this practice is the inability of the innovator firm to "track adverse events and complaints," he added.

Counterfeit active ingredients are a serious concern of the generics industry, which has difficulty in determining if a bulk chemical is genuine. India and China produce a large volume of counterfeit APIs, Grosse stated, noting that there is a large "financial reward" for counterfeiters.

The sale of counterfeit drug products worldwide is "increasing at a rapid rate," Grosse asserted. He cited figures suggesting that 40-60% of drug products sold in Malaysia and Indonesia, 25% sold in Mexico, and 7-8% sold in the U.S. are counterfeit.

Since not all countries cooperate with efforts to recall counterfeit products or investigate and prosecute counterfeiters, it is "impossible to stop these activities," Grosse maintained. He noted that countries are more diligent in punishing those dealing in illicit drug products than those counterfeiting legal drug products.

The current regulatory defenses against unethical and illegal practices are not adequately developed, Grosse said. Although U.S. Customs is "very much aware and very effective," he said, other enforcement agencies "have been very ineffective." Manufacturers are collecting "a lot of information" on the problem, he added, but "do not have a very good place to take it."

➤ In order to prevent a "catastrophe," Grosse contended, "enforcement has to be a cooperative effort" between FDA and other government agencies, the industry, and health care professionals.

He called on USP and FDA to work together to facilitate industry's use of new security technologies such as nontoxic tagging compounds that "readily" enable the identification of counterfeit products. According to Grosse, only "three products [are] on the U.S. market today" with tagging compounds, although many companies possess the capabilites to use them. The current regulatory constraints make employing tagging compounds "heavily burdensome," he commented.

FDA DRUG GMP UNTITLED LETTERS TO FOREIGN FIRMS IN FY 1997

The following is a list of untitled letters sent to foreign manufacturers by FDA in FY 1997. Included is the recipient's name, the location of the inspected facility, the date the untitled letter was issued and the date of the inspection, followed by a description of the cGMP problem area(s) addressed in the letter. Untitled letters are typically sent in lieu of warning letters when the products covered by the inspection are not yet marketed in the U.S.

Delmar Chemicals Location: Lasalle, Quebec, Canada Warning letter date: 7/28/97 Inspection date: 5/12-16/97 Product type: API	Out-of-specification investigations ▪ System suitability ▪ Equipment maintenance ▪ Validation of each current method ▪ Release test chromatography ▪ Equipment cleaning validation.

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Farmak Location: Olomouc, Czech Republic Warning letter date: 12/18/96 Inspection date: 10/21-24/96 Product type: API	Establishment of master process validation protocol ■ Process validation data showing that the manufacturing process is consistent ■ Establishment of impurity profile ■ Complete master production and batch production records.
Groups Lipha Location: Pithiviers, France Warning letter date: 5/19/97 Inspection date: 2/10-13/97 Product type: API	Out-of-specification handling for validation batches.
Lipha S.A. Location: Semoy, France Warning letter date: 5/09/97 Inspection date: 3/17-20/97 Product type: oral solids (tablets)	Specification in NDA/certificate of analysis of analytical methodology for assay and related substances tests on exhibition batches ■ Calibration of laboratory equipment, i.e., pH meters, analytical balances ■ Analytical procedures for water content in an acid solution in the raw material assay ■ Resolution of peaks in the assay of raw material and drug product ■ Specificity in process validation protocol regarding sampling technique, size and frequency.
Lipha S.A. Location: Semoy, France Warning letter date: 7/07/97 Inspection date: 4/22-26/96 Product type: sterile finished products	Adequate detail in SOP for media fill tests to assess, for example, interventions, filter changing, validation load size, and fill line speed.
Hoechst South Africa Location: Pretoria, South Africa Warning letter date: 11/06/96 Inspection date: 7/15-18/96 Product type: API	Validation of blending processes to demonstrate homogeneity within defined limits of commercial size lots ■ Establishment of theoretical yields and final batch sizes ■ Completion of master production/control records and batch production/control records ■ Out-of-specification result investigations ■ Laboratory records data derived from all tests necessary to assure compliance with established specifications and standards ■ Written procedures for stability program, environmental monitoring and recall procedures.
Mitchell Cotts Chemicals Location: West Yorkshire, Great Britain Warning letter date: 10/29/96 Inspection date: 6/10-12/96 Product type: API	Concurrent and retrospective process validation ■ Batch reprocessing ■ Out-of-specification result investigations ■ Equipment cleaning for multiple use equipment ■ Water system validation.
Novartis Location: Stein, Switzerland Warning letter date: 4/25/97 Inspection date: 7/10-19/97 Product type: sterile finished products	Facility and process design issues: aseptic connections ■ Open door impact on airflow ■ Floor to wall junctions ■ Out-of-specification result investigations for surface contamination ■ Quality control unit overview of qualification plans ■ SOP to notify quality control unit of filling line interventions and stoppages ■ Environmental monitoring program ■ SOPs for proper documentation of media fill validation runs ■ Validation of analytical methods ■ Particulate readings where loading/unloading occurs ■ Justification of micron filter selection for active air sampling.
Roquette Freres Location: Lestrem, France Warning letter date: 1/17/97 Inspection date: 11/4-7/96 Product type: API	Validation of manufacturing process ■ Batch record control and maintenance ■ Operating ranges in manufacturing processes ■ Out-of-specification result investigations ■ Use of EU monograph test method instead of USP test method.
Urquima Location: Barcelona, Spain Warning letter date: 10/30/96 Inspection date: 6/3-5/96 Product type: API	Process validation ■ Forced degradation studies.

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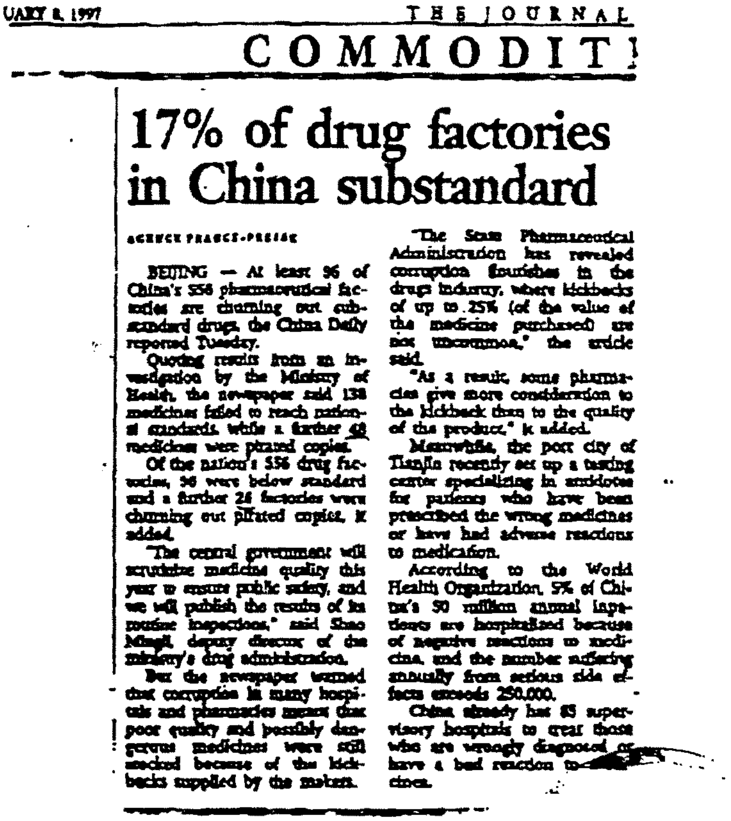


UARY 8, 1997

THE JOURNAL

COMMODIT

17% of drug factories in China substandard

AGENCE FRANCE-PRESSE

BEIJING — At least 96 of China's 556 pharmaceutical factories are churning out substandard drugs, the China Daily reported Tuesday.

Quoting results from an investigation by the Ministry of Health, the newspaper said 138 medicines failed to reach national standards, while a further 48 medicines were pirated copies.

Of the nation's 556 drug factories, 96 were below standard and a further 26 factories were churning out pirated copies, it added.

"The central government will scrutinize medicine quality this year to ensure public safety, and we will publish the results of its routine inspections," said Shao Mingli, deputy director of the ministry's drug administration.

But the newspaper warned that corruption in many hospitals and pharmacies meant that poor quality and possibly dangerous medicines were still stocked because of the kickbacks supplied by the makers.

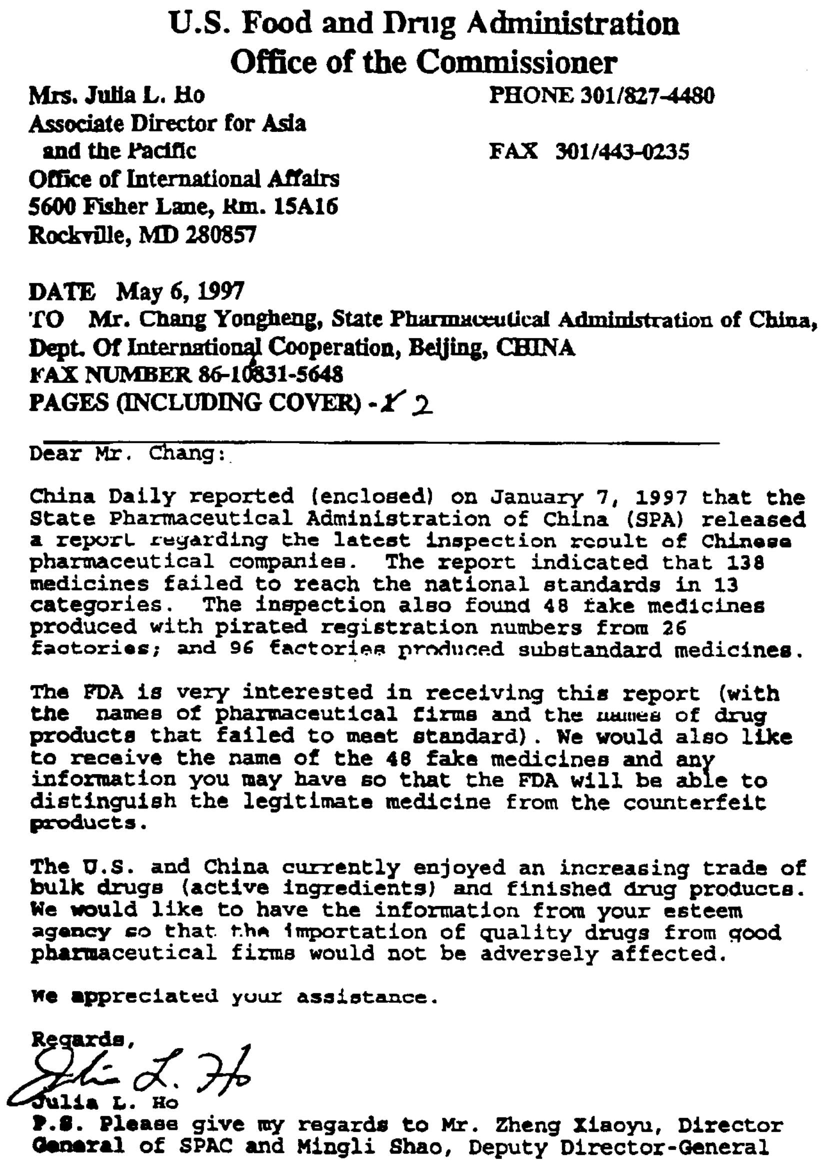
"The State Pharmaceutical Administration has revealed corruption flourishes in the drugs industry, where kickbacks of up to 25% (of the value of the medicine purchased) are not uncommon," the article said.

"As a result, some pharmacies give more consideration to the kickback than to the quality of the product," it added.

Meanwhile, the port city of Tianjin recently set up a testing center specializing in antidotes for patients who have been prescribed the wrong medicines or have had adverse reactions to medication.

According to the World Health Organization, 5% of China's 50 million annual inpatients are hospitalized because of negative reactions to medicine, and the number suffering annually from serious side effects exceeds 250,000.

China already has 85 supervisory hospitals to treat those who are wrongly diagnosed or have a bad reaction to [illegible]cines.



U.S. Food and Drug Administration
Office of the Commissioner

Mrs. Julia L. Ho
Associate Director for Asia
and the Pacific
Office of International Affairs
5600 Fisher Lane, Rm. 15A16
Rockville, MD 280857

PHONE 301/827-4480
FAX 301/443-0235

DATE May 6, 1997
TO Mr. Chang Yongheng, State Pharmaceutical Administration of China,
Dept. Of International Cooperation, Beijing, CHINA
FAX NUMBER 86-10831-5648
PAGES (INCLUDING COVER) -~~1~~ 2

Dear Mr. Chang:

China Daily reported (enclosed) on January 7, 1997 that the State Pharmaceutical Administration of China (SPA) released a report regarding the latest inspection result of Chinese pharmaceutical companies. The report indicated that 138 medicines failed to reach the national standards in 13 categories. The inspection also found 48 fake medicines produced with pirated registration numbers from 26 factories; and 96 factories produced substandard medicines.

The FDA is very interested in receiving this report (with the names of pharmaceutical firms and the names of drug products that failed to meet standard). We would also like to receive the name of the 48 fake medicines and any information you may have so that the FDA will be able to distinguish the legitimate medicine from the counterfeit products.

The U.S. and China currently enjoyed an increasing trade of bulk drugs (active ingredients) and finished drug products. We would like to have the information from your esteem agency so that the importation of quality drugs from good pharmaceutical firms would not be adversely affected.

We appreciated your assistance.

Regards,

Julia L. Ho

Julia L. Ho

P.S. Please give my regards to Mr. Zheng Xiaoyu, Director General of SPAC and Mingli Shao, Deputy Director-General

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF THE COMMISSIONER
SPECIAL ASSISTANT FOR INVESTIGATIONS
5600 FISHERS LANE, ROOM 15-44, HF-5
ROCKVILLE, MD. 20857

FACSIMILE TRANSMISSION RECORD

Number of Pages (including coversheet) 5

TO: Tom Gardine

Fax Number 43787 Phone Number

FROM: Jim Hunter, Special Investigations

Fax Number (301) 443-5262 Phone Number (301) 443-6955

DATE: 7/7/97 TIME:

MESSAGE: As discussed —

NOTE: This transmission is from a DEX 740 telecopier. If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the telephone number above.

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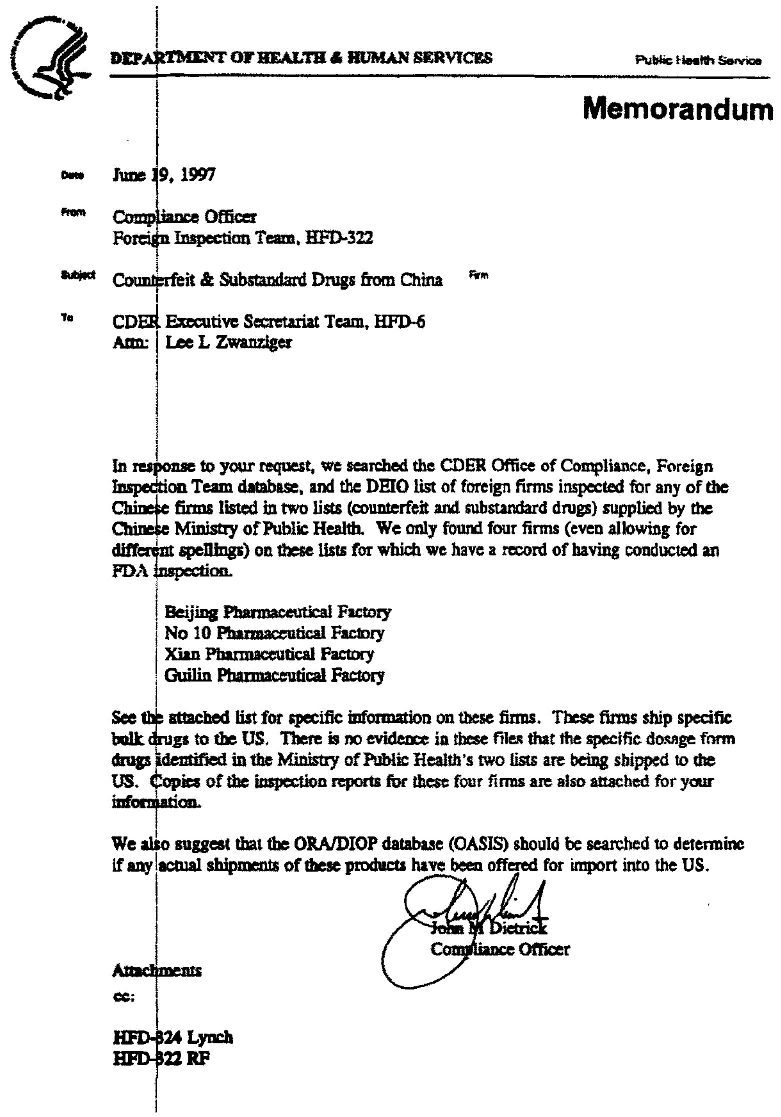

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date June 19, 1997

From Compliance Officer
Foreign Inspection Team, HFD-322

Subject Counterfeit & Substandard Drugs from China Firm

To CDER Executive Secretariat Team, HFD-6
Attn: Lee L Zwanziger

In response to your request, we searched the CDER Office of Compliance, Foreign Inspection Team database, and the DEIO list of foreign firms inspected for any of the Chinese firms listed in two lists (counterfeit and substandard drugs) supplied by the Chinese Ministry of Public Health. We only found four firms (even allowing for different spellings) on these lists for which we have a record of having conducted an FDA inspection.

Beijing Pharmaceutical Factory
No 10 Pharmaceutical Factory
Xian Pharmaceutical Factory
Guilin Pharmaceutical Factory

See the attached list for specific information on these firms. These firms ship specific bulk drugs to the US. There is no evidence in these files that the specific dosage form drugs identified in the Ministry of Public Health's two lists are being shipped to the US. Copies of the inspection reports for these four firms are also attached for your information.

We also suggest that the ORA/DIOP database (OASIS) should be searched to determine if any actual shipments of these products have been offered for import into the US.

John M Dietrick
Compliance Officer

Attachments
cc:

HFD-324 Lynch
HFD-322 RF

List of Unqualified Medicines:

1. Hydrochloric lidocaine injection [none]
2. Vitamin C Tablets

   Beijing Pharmaceutical Factory

   We have a Beijing #2 Pharmaceutical Factory in Beijing, Chao Yang District. It is approved for bulk sulfamethazine which is the only product shipped to the US. The report does sya the firm also maufactures tablets, capsules, powders, and liquids (including analgesics and vitamins)for sale in Europe, China, and Latin America.

   No. 10 Pharmaceutical Factory, Chengdu City, Sichuan Province

   We have a Sichuan Pharmaceutical Co., Ltd. At 1 Shanbanquio Rd., Ghengdu city, Sichuan province (CFN 9611834) This is a bulk antibiotic manufacturer last inspected 4/96. There is nothing in files to indicate firm manufactures vitamin C. US Agent is Flavine International, Closter NJ.
3. Acetylyl salicylic acid tablets [none]
4. Chlorpheniramine tablets [none]
5. Radix helicteris powder [none]
6. Agastache rugosa liquid [none]
7. Agastache rugosa decoction [none]
8. Agastache rugosa capsules [none]
9. Nitrogen tablets [none]
10. Hydrochloric rennin capsules [none]
11. Blastosphere tablets [none]
12. Lactic hibernaculum injection [none]
13. Acetyl spirochaeta tablets [none]

List of Medicines which have been counterfeited:

1. Vitamin C tablets

   Xian Pharmaceutical Factory, Shanxi Province

   We have a Xian Pharmaceutical Factory in Xian city, Shaanxi province, CFN 9611394. This firm was last inspected in 5/96 and manufactures both bulk and finished drugs. Only bulk tetracycline has been exported to the US and has been the only product inspected by FDA. A 1985 inspection report does mention that the firm manufactured ascorbic acid produsts. The US Agent is The China MEHECO (USA), Inc, Wayne, NJ. The firm is owned by the Chinese government.

2. Acetyl salicylic acid tablets

   Guilin Pharmaceutical Factory, Guangxi Province 951201, 9612554

   We have a Guilan Pharmaceutical Works in Guilin city, Guangzi province CFN 9612554. This was last inspected 8/94 as a bulk antibiotic and anti-microbial drugs manufacturer. A product catalog in the file does indicate this firm manufactures aspirin tablets, but there is no indication that they are for US distribution, and have not been covered during FDA inspections. The firm's US agent is Chemworth, in Woodbridge, CN.

3. Acetyl salicylic acid tablets [none]
4. Chlorpheniramine tablets [none]
5. Radix helicteris powder [none]
6. Agastache rugosa liquid [none]

U.S.FOOD & DRUG ADMINISTRATION
Division of Emergency & Investigational Operations

Fax Coversheet

TO: Tom Gardine	FROM: Gary Pierce Director
FAX #: 301-594-3787	(301)827-5655 fax: (301)443-3757

Division Telephone Number
(301)827-5653

FAX (301)443-3757
or (301)443-6919

REMARKS: Tom - call Jim and he can explain the significance of this list. It is in followup to info that Jack Mitchell's office gave us.

DATE: 6/24/97

PAGES SENT: (This plus coversheet) 6

JUNE 20, 1997

NOTE TO GARY PIERCE

FROM JON W HUNT

CHINESE FIRMS FROM JACK MITCHELL'S OFFICE

The two firms which are suspect in the DEG matter;
1.) Anli Chemical Industry
2.) Taihong Huagong Chan, Dalian

These firms are not on our inventory nor are they on the lists submitted by Jack Mitchell's office.

On the lists submitted by Jack's office, six firms or similar firms appear on our inventory of Chinese firms inspected. The Breakdown is as follows;

A LIST OF UNQUALIFIED MEDICINES

Category 2. - Vitamin C
Biejing Pharmaceutical Factory, Beijing - Mitchell's list did not have city Name.
Category 11. - Blastophere Tablets
Hua Nan Pharmaceutical Factory #1, Changsah, Hunan Prov. - Mitchell's list included "of Guangdong Pharmaceutical Industry Corp." in the name and did not have a city name.
Category 12. - Lactic Hibernaculum Inj.
Taiyuan Pharmaceutical Works, Taiyuan - Mitchell's list had a different location and used "Factory" instead of "Works".

A LIST OF MEDICINES AND MANUFACTURERS THAT HAVE BEED COUNTERFEITED

Category 1.- Vitamin C
Xian Pharmaceutical Factory, Shanxi Prov. - This firm has been inspected by FDA.
Category 2. - Acetyl Salicylic Acid Tablets
Guilin Pharmaceutical Factory, Guilin, Guangxi - This firm has been inspected by FDA.
Category 3. - Acetyl Salicylic Acid Tablets
Guangdong Pharma. #1, Guangzhou - Mitchell's list had a similar firm name, "Guan Dong Pharmaceutical Factory" at a different location.

These are the only similarities I could identify from the lists supplied by Jack Mitchell.

Beijing #2	Beijing, PRC
Changzhou Pharm	Changzhou, Jiangsu
Chi Feng Pharmaceutical Factory	Chi Feng City
Chifeng Pharmaceutical Factory	Chifeng
Chongqing #5 Pharmaceutical Factory	Chongqing
Chongquing Pharmaceutical Resch Inst	Chongquing, Sichuan
Fujian Institute of Microbiology	Fuzhou
Fuzhou Antibiotic Factory	Fuzhou, P.R.C.
Guangdong Pharm #1	Guangzhou, PRC
Guangxi Normal University	Guilin
Guangzhou Pharm Factory	Guangzhou
Guilin Pharm	Guilin, Guangxi
Haimen Pharmaceutical Factory	Haimen, Jiaojing
Haimen Pharmaceutical Factory	Jiaojing, Zhejiang
Hebei Pharmaceutical Factory	Tianjin, PRC
Hu-Nan Pharmaceutical Factory #1	Changsha, Hunan Prov
Hunan Pharmaceutical Factory #1	Hunan Province
Hunan Pharmaceutical Factory #1	Changsha, Hunan Prov
Jiangxi Pharm.	Nanchang, Jiangxi
Jicheng Pharmaceutical Factory	Shanghai 20071
Kun Shan Biochemical Production Fac	Kun Shan City
Lianyungang Pharmaceutical Factory	Lianyungang, Jiangsu
Long March Pharmaceutical	Leshan, Sichuan
Mongolia Ertok	
Mongolian Jin He Feed Proc. Factory	Inner Mongolia
Nanjing Pharmaceutical Factory	Nanjing
Nantong Pharm Factory	Nantong
Nantong Biochemical Pharm	Nantong
North China Pharm	Shijiazhuang
Northeast Pharm. Factory #6	Shenyang, Liaching
Northeast General Pharm Factory	Shenyang
Schezhen Chemical	Shenzhen, Guangdong
Shandong Xinhua Pharm Factory	Zibo, Shandong
Shanghai Pharmaceutical Institute	Shanghai
Shanghai Medicinal #15 Factory	Shanghai
Shanghai No 3 Pharmaceutical Factory	Shanghai
Shanghai Luodian Chemical Plant	Shanghai
Shanghai Pioneer Pharm	Shanghai
Shanghai #4 Factor	Shanghai, 200090
Shanghai #12 Factory	Shanghai
Shanghai #1 - Zhuanggiao Branch	Shanghai
Shanghai #6 Phar. Factory	Shanghai
Shanghai #17 Pharm	Shanghai
Shaoguan Pharm.	Shaoguan, Guangdong
Sichuan Pharmaceutical Co. Ltd	Chengdu
Sino-American Shanghai Pharm Ltd	Shanghai
Sunve Pharm. Baoling Factory	Shanghai
Sunve (Fmly Shanghai No 2)	Shanghai
Suzhou #4	Suzhou, Jiangsu
Suzhou Biochemical Pharmaceutical	Suzhou
SW Synthetic Pharmaceuticals	Chongquing
Taiyuan Pharmaceutical Works	Taiyuan
Tianjin Pharm	Tianjin
Tong Liao Ai Min	Tong Liao City

Weifang Pharm. #4	
Wenzhou Pharm Fact	
Xian Pharmaceutical Factory	Xian, Shaanxi Provin
Xin Xin Pharmaceutical Corp	Tianjin
Xinjiang Pharmaceutical Works	Xinjiang Prov
Yang Zhou Pharmaceutical Works	Yangzhou, Jiangsu
Zhejiang Haman	
Zhongxi Pharmaceutical Factory	

INTERNATIONAL AND TECHNICAL OPERATIONS BRANCH

CREATOR: Deborah Brown

COUNTRY: CHINA

CF NUMBER	FIRM NAME	CITY	STATUS	ESTABLISHMENT TYPE	LAST EI
[illegible]	WENZHOU PHARM FACT		A	B	
9610081	SHANGHAI #4 FACTOR	SHANGHAI, 200090	A	D	8/25/94
9610082	TIANJIN PHARM	TIANJIN	A	B	11/17/94
9610095	NANTONG BIOCHEMICAL PHARM.	NANTONG	A	D	5/14/87
9611046	LONG MARCH PHARMACEUTICAL	LESHAN, SICHUAN	A	D V	3/08/95
9611047	XIN XIN PHARMACEUTICAL CORPORATION	TIANJIN	A	B	3/28/96
9611048	HEBEI PHARMACEUTICAL FACTORY	TIANJIN, PRC	A	B	3/26/96
9611049	TAIYUAN PHARMACEUTICAL WORKS	TAIYUAN	I	D	11/11/88
9611391	BEIJING #2	BEIJING, PRC	A	B	8/02/94
9611392	YANG ZHOU PHARMACEUTICAL WORKS	YANGZHOU, JIANGSU	A	B	5/20/87
9611393	CHANGZHOU PHARM.	CHANGZHOU,JIANGSU	A	B	1/16/97
9611394	XIAN PHARMACEUTICAL FACTORY	XIAN, SHAANXI PROVIN	A	B	5/23/96
9611395	SHANDONG XINHUA PHARM. FACTORY	ZIBO, SHANDONG	A	B	4/26/96
9611396	NORTHEAST PHARMACEUTICAL FACTORY #6	SHENYANG, LIAONING	A	B	1/22/97
9611397	SHANGHAI #6 PHARMACEUTICAL FACTORY	SHANGHAI	A	D	11/09/95
9611399	FUZHOU ANTIBIOTIC FACTORY	FUZHOU, P.R.C	A	B	7/17/95
9611400	SUZHOU BIOCHEMICAL PHARMACEUTICAL	SUZHOU	I	D	8/10/87
9611831	SW SYNTHETIC PHARMACEUTICALS	CHONGQING	A	B V	11/09/94
9611833	GUANGDONG PHARM #1	GUANGZHOU, PRC	A	D	1/29/97
9611834	SICHUAN PHARMACEUTICAL CO. LTD.	CHENGDU	A	B	4/02/96
9611835	SINO-AMERICAN SHANGHAI PHARMA. LTD.	SHANGHAI	A	B	7/21/95
9611841	CHONGQING #5 PHARMACEUTICAL FACTORY	CHONGQING	A	D	8/13/96
9612406	SHANGHAI #12 FACTO	SHANGHAI	I	B	9/06/90
9612407	SHANGHAI #17 PHARM	SHANGHAI	A	D	9/05/90
9612408	SUNVE (FMLY SHANGHAI NO 2)	SHANGHAI	A	D	8/27/96
9612409	NANJING PHARMACEUTICAL FACTORY	NANJING	A	B	7/19/95
9612411	SHENZHEN CHEMICAL	SHENZHEN, GUANGDONG	I	B	9/20/90
9612412	SUZHOU #4	SUZHOU, JIANGSU	A	D	8/26/91
9612413	NORTH CHINA PHARM	SHIJIAZHUANG	A	D	6/19/91
9612414	JIANGXI PHARM.	NANCHANG, JIANGXI	A	B V	8/18/94
9612535	SHAOGUAN PHARM.	SHAOGUAN, GUANGDONG	I	D	8/28/91
9612547	HAIMEN PHARMACEUTICAL FACTORY	HAIMEN, JIAOJING	A	D	7/27/95
9612548	HAIMEN PHARMACEUTICAL FACTORY	JIAOJING, ZHEJIANG	A	B	7/27/95
9612552	KUN SHAN BIOCHEMICAL PRODUCTION FACTORY	KUN SHAN CITY	A	B	3/20/96

6/12/97 FIRM SUMMARY BY COUNTRY Page 2

INTERNATIONAL AND TECHNICAL OPERATIONS BRANCH

CREATOR: Deborah Brant

CF NUMBER	FIRM NAME	CITY	STATUS	ESTABLISHMENT TYPE	LAST EI
COUNTRY: CHINA					
9612533	TONG LIAO AI MIN	TONG LIAO CITY	A	D	
9612564	GUILIN PHARM	GUILIN, GUANGXI	A	D	8/05/96
9612595	SHANGHAI #1 - ZHUANGIAO BRANCH	SHANGHAI	A	D	3/12/96
9613752	MONGOLIA ERTOK		A	D	
9613753	NANTONG PHARM FACT	NANTONG	A	D,V	10/29/96
9613754	SHANGHAI NO 3 PHARMACEUTICAL FACTORY	SHANGHAI	A	D	
9613755	ZHEJIANG NAMEN		A	D	
9613757	WEIFANG PHARM. #6		A	D	
9613758	CHONGQUING PHARMACEUTICAL RESEARCH INST.	CHONGQUING, SICHUAN	A	D	5/21/97
9613759	GUANGZHOU PHARM FACTORY	GUANGZHOU	A✓	D	8/19/96
9613760	LIANYUNGANG PHARMACEUTICAL FACTORY	LIANYUNGANG, JIANGSU	A	D	11/06/96
9613777	HUNAN PHARMACEUTICAL FACTORY #1	CHANGSHA, HUNAN PROV	A	N D	
9613780	GUANGXI NORMAL UNIVERSITY	GUILIN	A	D	8/05/96
9613781	JICHENG PHARMACEUTICAL FACTORY	SHANGHAI 200071	A	D,V	3/09/95
9613782	MONGOLIAN JIN HE FEED PROC. FACTORY	INNER MONGOLIA	A	D,V	10/25/96
9613786	SUNVE PHARM. BAOLING FACTORY	SHANGHAI	A	D V	11/15/95
9613787	SHANGHAI MEDICINAL #15 FACTORY	SHANGHAI	A	D N,V	5/13/97
9613788	SHANGHAI PHARMACEUTICAL INSTITUTE	SHANGHAI	A	D	3/13/96
9613789	SHANGHAI LUODIAN CHEMICAL PLANT	SHANGHAI	A	D,V	3/14/95
9614292	FUJIAN INSTITUTE OF MICROBIOLOGY	FUZHOU	A✓	D	6/05/96
9614295	CHIFENG PHARMACEUTICAL FACTORY	CHIFENG	A	D	
9614298	NORTHEAST GENERAL PHARMACEUTICAL FACTORY	SHENYANG	A	D	6/17/96
9615430	ZHONGKE PHARMACEUTICAL FACTORY		A	D	
F960094	XINJIANG PHARMACEUTICAL WORKS (FACTORY)	XINJIANG PROVINCE	A	D	
F960095	HUNAN PHARMACEUTICAL FACTORY #1	HUNAN PROVINCE	A	D	
F960099	HU-NAN PHARMACEUTICAL FACTORY #1	CHANGSHA, HUNAN PROV	A	D	
F970061	CHI FENG PHARMACEUTICAL FACTORY	CHI FENG CITY	A	D	
F970137	SHANGHAI PIONEER PHARM.	SHANGHAI	A	D	

301-[illegible]

To: Susan Setterberg@REG@FDAORAMAR
Cc:
Bcc:
From: Fred Fricke@FCC@FDAORAMAR
Subject: Fwd: re: Fwd: bulk drug initiative
Date: Wednesday, November 15, 1995 14:43:35 EST
Attach:
Certify: N
Forwarded by:

- - - - - - - - - - - - - - Original Message - - - - - - - - - - - - - -

To: Fred Fricke@FCC@FDAORAMAR
From: Carl Nielsen@OCI@FDAOCIMET
Date: Tuesday, November 14, 1995 at 5:58:02 pm EST
Attached: None

Fred-
Some thoughts at the end of the day regarding Susan's comments:

- Importation of bulk drugs, Rx and OTC is virtually uncontrolled. Criteria for admissibility of an imported drug is not currently based on FDA approved status or evidence of authenticity. Rather, the agency only attempts to control importations based on drug listing information, which is not related to an FDA approved /validated process in an NDA, ANDA, NADA, ANADA, IND, or any other "D" word. Nor is drug listing necessarily related to a specific manufacturer of bulks. Any shipper can be drug listed..

- FDA domestic inspections do not include any meaningful procedures/examinations that may find or detect the use of counterfeit bulk drugs. Those procedures need to be developed and integrated into current inspectional/compliance programs. Historically, th
er systems at the finished dose manufacturer as it relates to a master/batch record. Those procedures alone will not detect counterfeits.

- Procedures for determining strategic sampling needs to be developed and implemented. The strategies will require analysis of import data, drug production data, drug costs, market conditions, drug patents, background checks of firms and individuals, drug experience reports, public and agency policy, forensic analytical capabilities (resources, including time), and investigational capabilities (resources).

- Ultimately, the initiative (investigations) needs to be done jointly with designated US Customs officials (preferrably Garrison)

- Confessed counterfeiter in Germany, in 1992, said at least 35% of bulk antibiotics exported to the USA is counterfeit.

- With this initiative, legitimate drug trade will be protected from competition from the criminal/illicit sector, and the country's drug supply will become safer.

- An FDA partnership with cooperating legitimate manufacturers of bulk drugs will enhance the effectiveness of the initiative by expiditing the sharing of critical, proprietary information necessary to determine the authenticity of a particular drug in a timely fashion so that appropriate administrative or legal action can be pursued.

Fred- this is all the gas I have for the day..Carl

To: Susan Setterberg@REG@FDAORAMAR
Cc: Carl Nielsen@OCI@FDAOCIMET
Bcc:
From: Fred Fricke@FCC@FDAORAMAR
Subject: re: bulk drug initiative
Date: Wednesday, November 15, 1995 10:28:04 EST
Attach:
Certify: N
Forwarded by:

Susan: Carl Nielsen and Ron Garrison(U.S. Customs) started the investigation of bulk drug counterfeiting in 1990. I have asked Carl to assist in preparing a response to your request. The drugs that we have analyzed and proved to be counterfeit are Oxytetracycline, Sulfamethazine, and Gentamycin Sulfate. There are numerous firms that are involved, but the only ones that are public knowledge are Flavine and Pennfield Oil. *** Carl should provide a confidential briefing for you.*** In addition to the above three drugs,Carl and Ron uncovered documentation to indicate that carbamazepine was counterfeited. Carl met with a Danish firm that supplied him with information about a large counterfeiting operation in Hamburg, Germany. This firm said that they had to stop producing Sulfamethazine because they could not compete with the large quantity of counterfeits coming from China. U.S Customs seized some of this Sulfamethazine in the U.S. The U.S. Customs also seized Oxytetracycline that was suppossed to be from an approved company in the former Yugoslavia but was counterfeit. These are separate incidents from the ongoing case against Flavine. Bulk Pergonal and Metrodine (fertility drugs) have been diverted or stolen and placed into counterfeit ampules. One person involved with this was found guilty in October. We are currently working with OCI and the company to find out where the counterfeiting operation is located. This may involve organized crime. In September U.S. Customs seized a shipment of bulk Ranitidine HCl worth 17 million dollars. Ranitidine HCl is the active ingredient in Xantac and Glaxo holds the patent. This Ranitidine was produced in India, entered the U.S. in Los Angles and was headed to Mexico thru Texas. Speculation says that it was to be used to produce counterfeit Xantac tablets which would then be smuggled into the U.S.

We have been in contact with several drug firms(eight) that indicated that they were aware of the counterfeiting problem as well as diversion of drugs. In some instances they mentioned specific drugs that have been counterfeited in other countries.

In addition to counterfeit drugs there are unapproved drugs. If these entries are checked against ITOB's database it will be a first step in preventing these from entering the country. There are some holes (data missing) in the database that needs to be fixed by CDER and the field.
The proposed funding for this project (in my opinion) is not inflated.
If it is only partially funded my recommendation is that the 3 OCI agents are essential and critical. One person is necessary to work with Bob Sharpnack. Possibly we could redirect some lab personnel from the bulk CDER program. As far as dollars, it will take considerably longer to analyze the samples because the existing instrumentation is almost in continuos use.

It appears that there are two different concerns regarding imported bulk drugs. The first is the quality,potency,adulteration,and sterility of the bulk drug from an approved supplier. I do not believe it is the function of the FCC to be involved in the analysis of these drugs, except by special request. The second is the counterfeit and unapproved bulk drugs. It is the function of the FCC to be completely involved in the analysis("fingerprinting") of these drugs. In fact the FCC should be the only laboratory analysing these samples because it requires the establishment of an authentic library, which is already in place, and the technology/expertise for fingerprinting is in place. It has been our experience that performing the USP tests will generally not lead to the detection of counterfeit bulk drugs.

BRIEFING PAPER

On

PRIORITY CONCERNS FOR BULK PHARMACEUTICAL CHEMICALS
with emphasis on Counterfeiting

JOSEPH X. PHILLIPS
Deputy Regional Food & Drug Director
Mid-Atlantic Region
Philadelphia, PA

PRIORITY CONCERNS

FOR

BULK PHARMACEUTICAL CHEMICALS

Counterfeiting

Unapproved Sources

Impurities

Process Validation

Cross Contamination

Release of Product
Failing to Meet Specifications

Counterfeiting

Definition: 21 USC 321 (g) (2)

The term "counterfeit drug" means a drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer,or distributor other than the person or persons who in fact manufactured, processed, pack, or distributed such drug and of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor.

Violation:

- FDA 21 USC 331 (i) (3)

  "The doing of any act which causes a drug to be a counterfeit drug, or the sale or dispensing, or the holding for sale or dispensing, of a counterfeit drug" is prohibited.

- US Customs law
  - FDA works closely with US Customs
- Joint Activities
  - Have seized products
  - Seized counterfeits cannot be re-exported; must be destroyed

  - Dosage forms made from counterfeits are also subject to regulatory action.

COUNTERFEITING

(continued)

Problem with Counterfeit BPC Products

- Safety cannot be assured
- Impurity profile is unknown and may vary, lot to lot
- Manufacturer is unknown
- No history of product
- No amount of testing can build quality into the product
- Age, storage, manufacturing environment, labeling, synthesis cannot be determined
- Negates R&D efforts and clinical trial research done on the legitimate BPC/Dosage form by legitimate manufacturers
- Creates real or potential health hazard.

COUNTERFEITING (CONT)

Chemicals for Focus

- To be identified
- In general, very expensive chemicals (relatively new entities) purchased in small quantities or less expensive chemicals purchased in very large quantities are particularly vulnerable to counterfeiting

Potential Participants in Illegal counterfeiting activity

- Manufacturer of BPC
- Manufacturers/Repackers who "launder" BPC's into counterfeit category
- Importers/Brokers/Domestic Agents
- Dosage Manufacturing Firms
  - Purchasing Agents acting essentially alone
  - Corporate Unit (if pervasive problem)

Problems in efforts to control imported BPC

- Drug Listing (21 CFR Part 207)
  - Used to determine admissibility
  - Anyone can obtain drug listing
  - Does not assure authentic material or source

- FDA inspectors/investigators need accessible information to help determine authenticity (topic to be expanded)

- Need to sensitize FDA inspectors/investigators/chemists to counterfeiting issues.

- Manufacturers of Dosage Forms need to be more diligent in their acceptance requirement criteria for BPC's and need to demand original Certificates of Analysis from suppliers.

- Suggested Organizations to Contribute to Strategy
    - FDA - ORO
    - FDA - OCI
    - FDA - CDER
    - FDA - Forensic Chemistry Center
    - US Customs
- Additional Sources of Assistance
    - To be expanded
    - Other FDA centers?
- Some Potential Strategies
    - Sensitize FDA Investigators/Inspectors to counterfeiting issues
        - Knowledge essential at dock side and during domestic or foreign drug inspections
    - Revisit "Listing" approach now used to decide admissibility of pharmaceuticals. Need more information to authenticate product and source.
    - Work with dosage form industry to get them to require original Certificate of Analysis from suppliers. Encourage them to develop more definitive acceptance testing.
    - Work with industry security units to develop intelligence.
    - Use small Multi-Disciplined committee to strategize approaches to deal with issues. Identify what has worked or is working and what has not been productive. Seek innovative ideas among committee. Evaluate focus of resources. Periodically evaluate implemented strategies so we remain focused.

Unapproved Sources

Problems

- Same as those for counterfeits but label reflects the correct unapproved source.

IMPURITIES

Too many products with little or no information about impurities.

BPC manufacturers need to identify impurities and to develop impurity profiles. This is required in new drug applications.

Impurities can represent a serious threat to the public health.

VALIDATION

- Manufacturing processes for BPC's should be validated.

- Analytical Methods should be validated.

CROSS CONTAMINATION

- Major concern to FDA and industry.
- Potential particularly high in non-dedicated equipment/facility.
- Lots manufactured in small scale with non-dedicated equipment are particularly vulnerable.
- Will be assessed during inspections.
- Impacts acceptability of clinical studies. (If cross contaminant is present)
- Need effective controls.

RELEASE DECISIONS

- Release of out of specs product without an adequate investigation or justification is suspect.

- Recent court decision impact

FAX COVER SHEET
FORENSIC CHEMISTRY CENTER
FOOD AND DRUG ADMINISTRATION
1141 CENTRAL PARKWAY
CINCINNATI, OHIO 45202
FAX NUMBER: (513) 684-6082

TO: LIZ BERBAKOS	FROM: FRED FRICKE

IF RE-TRANSMISSION IS NECESSARY
PLEASE TELEPHONE (513) 684-3501, EXT. 184 OR 185

65-846

NUMBER OF PAGES 1 (EXCLUDING COVER SHEET)

- 80% of Bulk Pharmaceuticals (active ingredients) are produced overseas.
- We have detected human and animal, bulk and dosage counterfeit pharmaceuticals.
- Flavine Corp. a major broker of bulk drugs was prosecuted in April for importing counterfeit Gentamicin, oxytetracycline, sulfamethazine. As part of a plea agreement, Flavine reported they also imported counterfeit methyldopa, carbamazapine, tetracycline and trimethoprim. Large shipments of sulfamethazine and oxytetracycline were seized and destroyed by U.S. Customs after FDA proved they were counterfeit.
- China and India are large suppliers of counterfeit/unapproved drugs. Known routes are: China/Hong Kong/Hamburg - US, China - US, India/Brussels/Amsterdam/Hamburg - US, India - US
- 17 million dollars of unapproved bulk cimetidine was seized in Dallas. The bulk which was seized by US Customs was produced in India, entered the US at Los Angeles - and was headed to Mexico to be turned into tablets and probably smuggled back into US.
- There is a large idle bulk pharmaceutical production capacity in Mexico and around the world that will likely to be used to produce counterfeit or unapproved bulks.
- Several companies including Hoffman-LaRoche, Merck, Eli Lilly, and Warner Lambert have briefed us on some of their products that have been counterfeited.
- We literally have no control over bulk drugs that enter the US. The only requirement to import a drug that our import investigators and US Customs routinely check via computer is called a drug listing. Anyone can obtain a drug listing.
- Counterfeit or unapproved bulk drugs can unknowingly be received by legitimate dosage form manufacturers and turned into tablets/capsules and sold as legitimate drugs. These drugs can reach anyone including the President.
- Some members of the generic industry and possibly some innovator firms are knowingly receiving counterfeit and unapproved drugs.
- Import brokers (US Agents) are dealing in counterfeit or unapproved drugs.
- We are working on developing ways to detect counterfeits and unapproved drugs.
- We have a joint project with the United Kingdom's Medicines Control Agency to detect counterfeit drugs.
- It appears that we have just scratched the surface of the problem of counterfeit drugs and will need considerable assistance in getting the problem under control.

UNITED STATES GOVERNMENT
Memorandum

DEPARTMENT OF THE TREASURY
UNITED STATES CUSTOMS SERVICE

DATE: July 29, 1996

FILE: KC08PR92KC0006

TO : Assistant Director, Operations
Fraud Investigations Division

THROUGH: Special Agent in Charge
Chicago, Illinois

FROM : Resident Agent in Charge
Kansas City, Missouri

SUBJECT: Operation CDI (Counterfeit Drug Investigations)
Special Project Proposal FY97

The attached proposal is forwarded with a recommendation for approval. This effort has been successful thus far. Attachment 1 to this memo identifies the successful prosecutions developed from this case. All the defendants are currently awaiting sentencing. This project was a headquarters funded project in FY92 and FY93. All funds requested, as in the prior years, are travel related.

Special Agent [redacted] has developed a certain amount of expertise in this area. His participation in a FDA sponsored counterfeit task force has been requested by the FDA. What is envisioned here is a natural extension of the knowledge and contacts developed thus far. This issued is a serious Public Health concern and it cannot be ignored. Customs was the lead agency in the investigation of Flavine International and we should continue in that lead role.

James L. Lewis

attachments

FEDERAL PROSECUTIONS
FROM OPERATION CDI

DEFENDANT	CHARGE	PLEA
Timothy Sommer	Mail Fraud	Guilty
Ira Siegel	Money Laundering	Guilty
Uziel Goldfeld	Money Laundering	Guilty
Gerd Weithase	Conspiracy to Commit Money Laundering	Guilty
	Conspiracy to Distribute Counterfeit drugs	Guilty
Wolf Vogel	Smuggling	Guilty
John Milhard	FDA Violation	Guilty
Fred D. Wall	Mail Fraud	Guilty
Flavine International	Conspiracy to Commit Money Laundering	Guilty
	Conspiracy to Distribute Counterfeit Drugs	Guilty

AWAITING CHARGES:

Mark Paradise	Smuggling

OPERATION CDI

INTRODUCTION

This document proposes a joint investigative effort between this office, the FDA's National Forensic Chemistry Center and FDA's Office of Criminal Investigation. It is predicated upon the successful conclusion of the investigation of Flavine International. Information developed from that investigation and information developed independent of it reveals a specific need for investigation action. As a result of that investigation it was determined that a real need exists for extensive and intensive examination of bulk pharmaceutical raw material importations for counterfeit drugs. The use of counterfeit pharmaceutical raw material in the production of drugs jeopardizes the efficacy and safety of the drugs. The safeguards imposed by the drug approval process are violated. There is no assurance that drugs made from counterfeit raw material will do what they are supposed to do. More significantly, the use of counterfeit raw material may introduce harmful impurities or create chemical interactions that would not exist in drugs produced from product from approved raw material manufacturers. It appears that a counterfeit raw material supplied by Flavine International was used to create an anti-convulsant drug used to treat epilepsy. Several epileptics died as a result of seizures while taking the drug made from the counterfeit product. Some epileptics suffered seizures while taking the counterfeit drug but did not die. When their medication was changed from the suspect counterfeit product their seizures were brought under control. This creates a serious Public Safety issue and must be aggressively investigated.

PROBLEM

Counterfeiting of pharmaceutical raw material will occur if non FDA approved source material is labeled and packaged as FDA approved material and entered into the Commerce of the United States. The FDA has a procedure by which foreign and domestic pharmaceutical raw material manufacturers register their product and manufacturing processes with the FDA and receive a Drug Master File. This approval process allows the product to be used in drugs manufactured and dispensed in the United States upon satisfactorily complying with FDA regulations and approvals. The counterfeiters will obtain non FDA approved material, create labels of FDA approved and registered foreign manufactures and affix those labels to the non approved material and represent that relabeled product as the approved product. It is known that this counterfeiting occurs in Hamburg, Germany, and Hong Kong, however, it has occurred within the United States. The substitution of unapproved material for approved pharmaceutical active ingredients is the counterfeiting process this initiative seeks to address.

The dimension of the problem can be best summarized by the following observations. The U.S. Customs Service made four seizures of counterfeit bulk pharmaceutical raw material in 1991 destined to Smith Kline Beecham, Omaha, Nebraska. The total amount seized was 76,500 kilograms valued at approximately $1,500,000. The material seized was supplied by three different U.S. importers. Ultimately, this office was involved in the prosecution of Flavine International, who was not one of the three importers from which product was seized. Flavine had been supplying Smith Kline Beecham with counterfeit material since 1985. The material supplied by Flavine had a value of approximately 5 million dollars. None of the material supplied by Flavine was seized. Therefore, it can be concluded that Smith Kline Beecham received counterfeit material on just one drug from at least 4 different U. S. importers.

Further, we have been able to determine that Flavine International supplied at least 9 different counterfeit bulk pharmaceutical active ingredients. The victim drug companies manufacture both human and animal drugs. Although we cannot be certain, it appears that Flavine stopped importing counterfeit drugs in 1992. The last known importation of counterfeit by Flavine International occurred in 1992. We know that Flavine supplied counterfeit drugs to at least 6 different U.S. drug manufacturers.

In a related investigation, we were able to document the activities of another U.S. bulk drug importer. This importer supplied counterfeit bulk material to many of the same U. S. drug manufacturers described above. In addition, this importer supplied counterfeit material to at least four U. S. drug manufacturers, not previously identified. We were able to seize approximately 60 metric tons of counterfeit material supplied by this importer in July 1992. In September 1992 we seized an additional 14 metric tons of counterfeit material from another drug manufacturer, which was also provided by this importer.

Based upon the above, we know of at least 5 U.S. importers that have sold U.S. drug manufacturers counterfeit bulk pharmaceutical material. We know that one of these importers counterfeited at least 9 different bulk drugs. We know that there were at least 9 U.S. drug manufacturers who received counterfeit material. We strongly suspect that the number of U.S. end users who received counterfeit is much higher. It would be folly to assume that we identified and prosecuted all counterfeit drug importers.

Consider this. Seventy to eighty per cent of all generic drugs are made from imported bulk pharmaceutical active ingredients. Sixty per cent of brand name drugs are made from imported active ingredients. The U.S. drug industry is dependent on imported materials.

This information is based upon knowledge developed from a 4 year investigation of just two importers of counterfeit drugs. A broader examination would have uncovered additional importers of counterfeit. What can be certain is that the importers had little regard as to where the counterfeit material was destined, either human or animal drugs.

Further, because of time constraints caused by the preparation of a case against Flavine International, we were unable to pursue all the suspect drugs uncovered in this investigation. We were fortunate that we discovered enough evidence associated with the one bulk drug that was seized at Smith Kline Beecham. We were able to build a case primarily on that evidence. Consequently, the focus of our investigation was limited to that very narrow area and to a large extent, limited to Flavine International. However, during the course of this investigation, and several others, a number of industry sources were developed, as well as a certain amount of expertise and knowledge of the industry. Based upon the guilty pleas by the defendants in the Flavine

International case and subsequent admissions confirming our suspicions about other drugs, and the knowledge developed, we have had the opportunity to re-examine the various pieces of information relating to other drugs and other importers. This re-examination has given rise to concern about the potential of other counterfeit importations. We believe that the problem could be significant.

Currently, the way that the imported bulk pharmaceutical drug industry operates is through U.S. agents like Flavine International. These agents represent foreign bulk drug manufacturers to U.S. end users and to the U.S. government, primarily the FDA, DEA and U.S. Customs. Generally, communications by the U.S. drug manufacturers and the FDA with the foreign manufacturers are conducted through the U.S. agent of the foreign manufacturer. The importers described in the first four paragraphs of this paper are the U.S. agents. Flavine International even counterfeited the product of a foreign manufacturer for which they were the 'exclusive' U.S. agent. The other agents described above counterfeited product from various approved foreign sources.

This counterfeiting occurs because of raw material demand. The U.S. end user paid the same price to the US agent/importer for counterfeit material as was paid for authentic bulk drug material. What drives the U.S. end user is the demand for the product. Even though they know who the U.S. agents are for specific foreign manufacturers, they'll place orders with other agents because of demand. What drives the counterfeiter is the profit that can be made from substituting counterfeit product for the authentic. Flavine was selling counterfeit to Smith Kline Beecham at $19.50 per kilo. This counterfeit was costing Flavine $12.10 per kilo. During this same approximate time, the designated US agent was also selling Smith Kline Beecham authentic material at $19.50 per kilo. The authentic material was costing the US agent $12.30 per kilo. The significance of this fact was that the US agent could get authentic material, Flavine could not. Smith Kline Beecham purchased from both Flavine and the US agent because of demand. U.S. importers may buy authentic bulk pharmaceutical product on the open world market if its available. If they can't obtain the authentic material, they'll substitute counterfeit. Approved foreign manufacturers know their markets. They do not produce tons of excess product to sell on the open market driving the price down. There is no guarantee that there will be buyers. Like other manufacturers they know their market and will generally try to develop long term contracts with their customers to provide some stability to their production process.

The drug product being sold to Smith Kline Beecham Animal Health was Oxytetracycline Base. This was not a sophisticated new drug product. It had been "generic" for a number of years. It was, however, a product for which Smith Kline Beecham was heavily dependent and had only one approved foreign source. Even though several approved foreign manufacturers existed, Smith Kline Beecham had sought and received authority from the FDA to use only one manufacturer for most of the period covered by the investigation.

The other counterfeit drug product seized by Customs and destroyed by the government was Sulfamethazine. This product is also used in the animal health industry and as an intermediate in the production of human drugs. This drug product is equally unsophisticated, having been "generic" for a number of years. However, on occasion it was in very short supply from specific manufacturers. The FDA has approved a number of foreign manufacturers for this drug.

These two drug products point out a very interesting anomaly, the counterfeiters didn't focus on just human drugs, nor did they select the latest product to become "generic." These two drug products would not appear on a list of the top 25 imports, they probably wouldn't make the top 100. What they do suggest is that virtually any drug product can be counterfeited. The two drugs products that we were able to identify and seize as counterfeit were not the latest drugs to come off patent protection. These two drugs have been in the generic arena for a number of years. The President of Flavine International admitted that his firm counterfeited a number of human drug products, some of them very significant drugs. He admitted to counterfeiting tetracycline in early 1982. This occurred after a PRC firm received approval from the FDA. That PRC firm could not satisfy the US demand for its tetracycline and Flavine International was not the US agent.

However, industry sources have advised me that certain drugs, because of demand and timing and the type of drug, would definitely be on their suspect list. An example of such a drug would be Cimetidine. This product, recently entered the generic arena because of the expiration of patent protection, is virtually everywhere. You cannot have escaped the plethora of advertisements, printed and televised, regarding the various ulcer treatments now available, many with reduced potency as OTC. This creates the requisite demand for counterfeit.

Although this is a highly regulated industry, there are numerous loopholes and regulation short comings. Chief among these are the controls on imported bulk pharmaceutical raw materials. In a perfect world the regulations in place would probably suffice. Unfortunately, we do not live in a perfect world and there are many who would take advantage of any weaknesses in the system. We cannot totally change the way the system works, but we can improve the system. More importantly for OI, we can become more active in detecting and identifying those who would abuse the system.

The FDA requires that suppliers of drug raw materials have Drug Master Files. This includes foreign manufacturers. U.S. drug manufacturers reference these Drug Master Files in their submissions to the FDA for drug approvals. Those foreign manufacturers who go to the trouble and expense of bringing their manufacturing practices up to the standards necessary to obtain a Drug Master File, will have the opportunity to sell their approved products in the U.S. market, the richest market in the world. A violation occurs when importers knowingly substitute and label an unapproved product as an approved product. This results in a misbranded/counterfeit drug product that has been described on the entry documents as being manufactured by an approved manufacturer. In fact, it may not have even been manufactured in the country where the approved manufacturer is located. Because of the heavy regulatory nature of this industry due to FDA requirements, counterfeiting requires false invoices, false labeling on the product, false Certificates of Analysis describing the product and, depending on the sophistication of the counterfeiters, possibly false seals and packaging. Some of the counterfeiting is unsophisticated. However, some of it is so sophisticated that it may go undetected.

GOAL/OBJECTIVE

The goal of this effort is to identify, apprehend and prosecute importers of counterfeit bulk drugs. Although this will not be easy, it is possible. The investigation of Flavine International has shown what can be done. At a minimum, with each finding of counterfeit drug there will be a violation of the Smuggling statute. The investigation of Flavine International started when one FDA employee became aware of discrepancies between the drums of the authentic manufacturer and those of counterfeit shipments. We have learned a great deal since that discovery. The defendants in that case have plead guilty to smuggling, conspiracy to smuggle, conspiracy to commit money laundering and to certain FDA violations.

1. To identify importers of counterfeit pharmaceutical raw material.

2. To seize importations of counterfeit pharmaceutical raw material prior to that material being used in the manufacture of drug products.

3. To secure the necessary evidence to successfully prosecute those identified with violations of Title 18 USC 371, 542, 545, 1956 and 1957 and Title 21 USC 321 and 333.

4. To identify all assets and seize those that can be traced to the money laundering aspects of the fraudulent importations.

5. To educate the pharmaceutical industry that this type of public health endangerment will not go unpunished.

OBSTACLES

Because the entries are made by the US agent/importer and not the US drug manufacturer we need to establish a method to connect drug imports to the end users. We can identify drugs through ACS data files, and in so doing, put the bulk drugs in the importers hands. We must go the next step and put the drugs in the end users facility. We must overcome this break in the transportation chain. Through close cooperation with the FDA this can be done.

Entries of product from foreign manufacturers by someone other than the appointed US agent would be a strong indication of a potential problem. There lies a strength to this plan. In order to identify where the material imported by someone other than the US agent is going, we have to know which US drug manufacturer is authorized to use the material in the first place, and then, we would have to know whether they have ordered from the non authorized US agent. Unfortunately, that has occurred numerous times in the past by several different end users. The Smith Kline Beecham example cited earlier is a prime example. We have found numerous shipments of unapproved product identified as approved product shipped by someone other than the designated US agent.

The solution to the immediate problem of identifying where suspect material shipped by non US agents to US end users can be overcome. This information can be obtained by Search Warrants, contact with the end users, or industry sources. The Search Warrant mechanism is the preferred method, but unfortunately we will not have the PC in the beginning. That leaves contacting the end users and industry sources and the investigator's knowledge. In the past these methods have proved very successful, however they are not without certain drawbacks. The first of these is that by contacting the end user, it becomes more difficult to charge them as a target if evidence of wrong doing is developed. Secondly, unless the request for information to the end users is worded very carefully, you may disclose information that will be conveyed innocently or intentionally to the targets of the investigation.

US agents/importers of foreign bulk pharmaceutical products comprise a relatively small number of firms. Employees of these firms develop a certain expertise that is confined to this industry. Employees of these firms transfer back and forth frequently. The firms all deal with the same, finite number of drug manufacturer end users and foreign sources of supply. Rumor mongering seems to be endemic to this industry. There are several industry publication which have sections that cater to "gossip." During the Flavine investigation I intentionally planted a false rumor to a target of the investigation, a drug importer. Later that day, the rumor was repeated back to me as gospel from another source, a drug manufacturer, located in a different state. Obviously, we have to be careful what information is disclosed and how the information is packaged.

But, we were successful in the past and should be equally successful in the future.

The targets of our investigation will come from the following areas. The following steps are not listed in order of priority.

1) From our previous investigation, and from industry sources, the names of several domestic agents and foreign shippers have been acquired who have a reputation of questionable practices. Efforts are underway to obtain further identification of these firms and individuals as well as others. Once they are obtained surveillance will be initiated on their shipments to determine the quantity and type of bulk pharmaceutical material they are importing or shipping to the US as well as the recipient of this material.

2) We have identified the top 30 generic drug imports for 1993 and 1994, (EXHIBIT A). Although this list is fairly encompassing, we have also identified certain other drugs that bear scrutiny based upon knowledge developed from our past investigative effort and industry sources. From this list we intend to apply investigative surveillance to the bulk drug imports. First we will identify the approved foreign manufacturers and their US agents of these 30 drugs. Then we will query the drug through ACS to determine if anyone else is importing the product. If the importation is by a source other than the appointed US agent, it bears scrutiny.

DATA FILES AVAILABLE

The following systems of records are available for use. Some of these systems have certain inherent problems.

1. The Drug Master File will contain reference letters from end users identifying which end users have, at least, referenced the bulk manufacturers as a potential source of the end users raw material. If the past investigations are used as an example, we will find more than one bulk material referenced by the end users. The end users will want more than one source for raw materials to respond to market and political conditions, i.e., problems with trade with the PRC. The Drug Master File will also identify the 'official' US agent for the foreign bulk drug

manufacturers. There are instances where we have found several US agents identified by a foreign drug manufacturer as their US representatives, sometimes for different products, and on occasion, for the same product.

2. Abbreviated New Drug Application (ANDA). We have received several ANDA listings from the FDA. The picture is far from clear. Flavine International is listed as an Approved Bulk Antibiotic Drug firm for 4 drugs. Flavine International does not now have, nor ever had an approved drug manufacturing facility. Other drug importers are also listed as bulk drug manufacturers. Other foreign shippers, who have no manufacturing capability also possess ANDA's. The mere possession by an entity of an ANDA does not necessarily mean that entity also possesses a manufacturing plant.

3. FDA Product Code. A great concept, but it fails miserably in execution. From what I've been able to learn is that the FDA Product Code, which is affixed to every product that the FDA regulates, has not been updated in a number of years. Therefore, drugs created in the last 15 years fall under a general catch all and are not specific as to the drug. This system, by itself, is not very useful in identifying drugs. However, used in conjunction with the TSUSA, it does help narrow the field.

4. National Drug Code (NDC). This number, issued by the FDA as part of the Drug Listing Act, lends an aura of respectability to the uninformed. Although there may be a legitimate purpose for the number, in practice it provides a means to counterfeiters to disguise the origins of the imported bulk material. Flavine International was convicted of counterfeiting, yet Flavine Germany has 77 drug listings and Flavine Hong Kong has 17 drug listings. Neither firm has drug manufacturing capability. What's more, another firm controlled by the president of Flavine, located in Liechtenstein had 14 drugs listed. As a matter of course Flavine had drugs listed so that they could import drugs under their own letterhead and referencing their own NDC without having to identify the actual drug manufacturer. These numbers were present on all of the Flavine invoices used at the time of entry. Consequently, attempts by Customs or the FDA to verify the product at the time of entry by the use of this number would have resulted in a match showing Flavine had, in fact, registered the product.

5. **Harmonized Tariff Schedule of the United States.** The TSUSA numbers are equally liberal in their application. They are generally not specific as to a drug, only to a general class of drugs. The Harmonized TSUSA is consistent with the world tariff classifications up to 6 digits. A TSUSA number can cover a multitude of drugs and many will fall into a general catch all.

To illustrate the problems described above, I queried ACS in an attempt to locate all entries of bulk cefaclor. To find all the variations of the drug I used the 6 numbers of the TSUSA and the first 5 numbers of the FDA Product Code. This was done to narrow the search parameters as much as possible while at the same time capture as much information as possible. The combination captured not only the cefaclor entries, but also entries of propylene glycol, talc powder, mannitol special, magnesium stearate and my favorite, "pharmaceuticals". Now, undoubtably with some work, a query could be devised that would eliminate most of the non cefaclor entries. However, it would also possibly eliminate some of the cefaclor entries.

The above data files offer some information, some of which is quite good. The data files used in conjunction with one another provide a means of locating suspect shipments. However, the search must be conducted by someone familiar with the industry and the players. Someone unfamiliar with the way that this industry conducts its business would not see the trees for the forest. As stated earlier, Flavine International counterfeited a product that it was the exclusive U.S. agent. If you would have assumed that no business would jeopardize their long term business by undercutting their own exclusive agency you would have assumed wrong. Yet such an assumption is defensible.

RESOURCE REQUIREMENTS

MANPOWER

As far as manpower requirements for this proposal, the initial commitment by the U.S. Customs Service is just one agent. The mission of this agent is to identify shipments of counterfeit bulk drugs and where they are going. What has been learned from the past investigation is a smaller investigative force is better. We don't need an army. Cooperation with the FDA is the key. The relationship develcped between this office and the FDA's National Forensics Chemistry Center and personnel of FDA's Office of Criminal Investigation played a key role in the successful prosecution of Flavine.

Now the goal is a little different. We want to focus on identifying the counterfeiters. We want to identify them and identify and seize their counterfeit shipments. At some point the investigation and prosecution will be turned over to whatever Customs Office of Investigation and FDA Office of Criminal Investigation that has geographic jurisdiction. The investigation of Flavine from beginning to end took 4 years. With the resources being requested we cannot spend that much time on a single prosecution and let the other counterfeiters operate. What we are proposing to do is to identify the counterfeiters and then move on to find the next one. But coordination must be maintained. Intelligence from one investigative effort must be carried forward and that is the continuum that this proposal offers. We would be available to provide whatever leadership and assistance that we can, but at some point the investigation and prosecution would be in the hands of the local area Agents in Charge. However, the intelligence gathering process would continue drawing from each new investigation and prosecution.

FUNDING

The principal funding need would be travel. Although pharmaceutical manufacturers are located all over the United States, a large number of them are located in Northeast. The bulk drug importers are primarily located in the Northeast. But this should not be viewed as a problem that is centered in the Northeast. The prosecution of Flavine International took place in Kansas City. Flavine relabeled drums in North Carolina. The seizures occurred primarily in the Midwest. Drug companies manufacturing facilities are located all over the United States. It is at these locations that much of the identification of counterfeit drugs will occur. This will include sampling, photographing product and drums, and inspection of documents. Further, it may be at these locations where the greatest prosecutive merit will lie.

At this point it is difficult to come up with a practical estimate of travel expenses. However, to give a basis to this proposal, certain trips have been identified as necessary. They are listed below:

Washington D.C. /Baltimore, Maryland

Liaison with FDA Headquarters/review of FDA documents. Senior Special Agent [redacted] has been asked to be a member of a FDA Bulk Drug Task Force with a focus on the importation of counterfeit, unapproved and bulk drugs (Exhibit B).

Liaison with DOJ Office of Consumer Litigation. The DOJ's Office of Consumer Litigation has prosecutive oversight of many FDA violations. Members of DOJ/OCL were the lead prosecutors in the counterfeit drug investigation of Flavine International. The U.S. Attorney's Office, Western District of Missouri, handled the money laundering investigation of Flavine International.

Air Fare:	$325 round trip		
Lodging:	$248	2 days @ 124 per day	
M&IE:	$76	2 days @ 38 per day	
MISC:	$100		
Total	$749		
	Four trips		$2996.00

New York/Newark

Contact with industry sources.

Air Fare:	$335		
Lodging:	$284	2 days @ 142 per day	
M&IE:	$76	2 days @ 38 per day	
MISC:	$100		
Total	$795		
	Four trips		$3180.00

Cincinnati, Ohio

Liaison with National Forensics Chemistry Center, FDA.

Air Fare:	$375	
Lodging:	$138	2 days @ 69 per day
M&IE:	$76	2 days @ 38 per day

MISC:	$100	
Total	$689	
	Two trips	$1378.00
	Total travel	$7554.00

Foreign Travel

During the investigation of Flavine International, Senior Special Agent [redacted] traveled to Hamburg, Germany, once to interview "Hamburg traders". This was a very fruitful trip, providing part of the education necessary to understand what transpires abroad. It also revealed the lengths that the counterfeiters will go to introduce their product into the US. Agent [redacted] also traveled to London, England, at the request of the British Control Agency, the British equivalent of the FDA, to speak at a panel discussion of counterfeit. Again, this was a fruitful trip, developing the overseas connections and exposure to the world wide threat that counterfeiters pose.

Although funding for foreign trips is not being requested at this time, it may be necessary to request additional funding in the future for that purpose. A return trip to the centers of counterfeiting, Hamburg, Germany, and/or Hong Kong, may arise. Further, a trip to the premises of an approved foreign manufacture may become necessary to prove counterfeit. A foreign source may want to cooperate, but be fearful of traveling to the US. These points became issues during the Flavine International investigation and are being mentioned now simply to provide a 'heads up'. Letters Rogatory to several countries were issued in the Flavine Investigation, and two have been issued in a spin off case. It may become necessary to travel foreign to facilitate those requests.

Miscellaneous Expenses

A second expense that will be encountered by this initiative is information. Like any other industry, the pharmaceutical industry as a number of professional journals and trade publications. Some I have managed to obtain free, others I have had to pass up because of expense. Further, some trade groups publish useful monographs. These however do have a cost. For that purpose I request a $1000 for books and publications.

Total Cost $8554.00

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*
* DELIVER TO: JAMES L LEWIS
*
*
* ORIGINAL
* SENT:          08/28/96  TIME: 12:55
* SUBJECT:       FUNDING APPROVAL-OF CDI/KC
* PRINT DATE:    08/28/96  TIME: 12:56
*
*************************************************************************

     TO:SACCH

     FM:RACKC

     SUBJ:HQ FUNDED PROJECT FY97-OF CDI

     THIS AM  I RECIEVED A PHONE CALL FROM FRAUD DIVISION STATING THAT
     THE PROPOSAL FOR  OF  CDI FOR  OCC 21/26 MONIES FOR FY97 HAD BEEN
     APPROVED THROUGH OI AND WAS AT BUDGET.

     OF CDI, COUNTERFEIT DRUG INVESTIGATIONS, WAS HQ FUNDED IN  FY  93
     AND 94. FOR FY97 WE REQUESTED OCC 21 AND 26 MONIES AS FOLLOWS:

     OCC 21  $7554.00

     OCC 26  $1000.00

     I HAVE NOT RECIEVED PAPER TO DOCUMENT APPROVAL.

     JIM LEWIS
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U.S. Food and Drug Administra
Office of Criminal Investigations
Metro Washington Field Office

Memorandum

Date May 15, 1996 File:

From Carl Nielsen, SA

Subject Counterfeit Imported Human Rx Bulk Drugs

To Frank Forgione, SAIC

In March, 1996, defendants in OCI Case No. 93-KCK-550-011J, Flavine International, entered guilty pleas pursuant to plea agreements and are cooperating with the government. Debriefing of the defendants has confirmed that for several years several bulk drugs were counterfeited and sold for use in the manufacture of human prescription generic drugs. Attached is a copy of the ROI for Case No. 93-KCK-550-011J covering the period 12/29/95 - 3/27/96.

The counterfeit human bulk drugs supplied to the generic drug industry by Flavine include carbamezapine (anti-convulsant), methyldopa (anti-hypertensive), gentamicin sulfate (anti-bacterial), tetracycline (anti-bacterial), trimethroprim (anti-bacterial), and sulfamethoxazole (anti-bacterial). Trimethroprim and sulfamethoxazole are often combined into a finished dosage form for the treatment of urinary tract infections.

It appears there have been deaths associated with the use of the generic prescription drugs made from the counterfeit bulk drugs supplied by Flavine International. There are records related to the generic drug manufacturer, Pharmaceutical Basics, Inc., (PBI) that indicate several epileptics died as a result of seizures while being maintained by carbamezapine made from counterfeit material. Epileptics who were not controlled by the counterfeit carbamezapine and did not die, reportedly became controlled when administered another brand of carbamezapine. Substantiating records should be available at the FDA Denver District office. The Denver District conducted the investigation of PBI.

When SA Dennis Riley and I were reviewing Flavine records in January through March, 1993, we found a copy of a wrongful death suit filed against Flavine in the State of Texas. The suit related to the use of a prescription combination drug containing trimethroprim and sulfamethoxazole made from bulk drugs supplied by Flavine. Besides counterfeiting trimethroprim and sulfamethoxazole, Flavine defendants have admitted to the unauthorized manufacture of bulk sulfamethoxazole in North Carolina which was supplied to several human generic drug manufacturers. Those drug companies include:

History of Imported Counterfeit Bulk Drugs

Counterfeit bulk drugs were first discovered in the U.S. marketplace in May, 1991, by CSO Micheal Spangenberg. He discovered the counterfeit Long March oxytetracycline because he had first hand knowledge of the authentic product which he obtained during an inspection of the Long March facility in China. FDA systems of operation did not detect the counterfeits. He found the counterfeit product at a Smith-Kline Beacham Animal Health facility in Omaha, NE, while conducting unrelated official business.

Smith-Kline had a large demand for oxytetracycline and purchased material purported to be Long March material from several suppliers, including Flavine International. In June, 1991, a joint FDA/USCS investigation began. During the course of the investigation USCS conducted multiple seizures of various counterfeit bulk drugs found in the veterinary drug industry. It was discovered that the suppliers of counterfeit bulk veterinary drugs also conduct business in the human bulk drug trade. However, strategically, largely because of limited resources, the direction of the investigation could not be changed from veterinary drug products to the human drugs without seriously jeopardizing a successful outcome of a case based on confirmed counterfeit veterinary drugs.

Consequently, when search warrants were executed at Flavine and CPB, International, in 1993, the scope of the warrants was limited to the government's knowledge of the veterinary drugs, even though many of the drugs, especially the antibiotics/anti-bacterials such as tetracycline, gentamicin sulfate, sulfamethoxazole, etc., also had/have application in the human drug industry. So, with these limitations, counterfeit gentamicin sulfate supplied by Flavine was the only prescription drug that could be traced to a human drug manufacturer (Solopak, Chicago, IL).

Definition of Counterfeit Bulk Drug

21 USC 321 (g)(2) defines counterfeit drug as follows; "The term counterfeit drug means a drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark**of a drug manufacturer**other than the person or persons who in fact manufactured **such drug**".

"The doing of any act which causes a drug to be a counterfeit drug, or the sale or dispensing, or the holding for sale or dispensing, of a counterfeit drug" is prohibited pursuant to 21 USC 331(i)(3).

So far, the investigations of imported counterfeit bulk drugs have found the counterfeits to be drugs from an unknown or unapproved source which have been labeled as being made by an FDA approved firm. Counterfeit material is good enough to pass identity tests for the ingredient.

Summary of FDA Requirements of U.S. Manufacturers of Human Generic Prescription Drugs

Holders of approved New Drug Applications (NDA's) and Abbreviated New Drug Applications

(ANDA's) had to validate the manufacturing process using the bulk drugs from each source identified in the NDA/ANDA. The firm is required to notify FDA of significant changes in the manufacturing process. And depending on the various factors considered by FDA, a significant change may require the firm to re-validate the manufacturing process or otherwise demonstrate that the change will not adversely effect the efficacy and safety of the finished product. The use of a bulk active ingredient from a source other than the one(s) used and described in the NDA/ANDA constitutes a significant change that could adversely effect the efficacy and/or safety of the finished dosage form.

The majority of generic finished drugs are made with bulk active ingredients made by foreign firms. CDER determines whether the foreign source referenced in the NDA/ANDA is capable of manufacturing bulk drugs in compliance with principles of current good manufacturing practices and compendia/monograph requirements. FDA approval or acceptance of the foreign source is based on the findings of foreign GMP inspections conducted by FDA and CDER's review of files (Drug Master Files, et al.) and other records submitted by the foreign firms. Typically the files and records are submitted to FDA/CDER via a U.S. agent designated by the foreign firm. All FDA correspondence is typically directed through the U.S. agent.

Dangers of Using Counterfeit or Unapproved Bulk Drugs in the Manufacture of Finished Drugs

The use of counterfeit and/or unapproved bulk drugs in the manufacture of finished drugs essentially invalidates any prior attempt by a firm to design, implement, and maintain a reliable manufacturing process based on sound quality assurance principles. Bulk drugs from unknown sources may introduce harmful impurities to the finished product. Some of the manufacturing steps , such as tablet compression, may not work well because of physical variances in the counterfeit drug. One might expect to see problems with dissolution of the finished drug. CDER chemistry reviewers have advised me that the use of counterfeit bulk drugs could result in potency and stability problems with the finished dose. In short, the use of counterfeit or unapproved bulk drugs jeopardizes the efficacy and safety of the drugs, i.e., there is little assurance the drugs will do what they are supposed to do.

Lack of FDA Control of Imported Bulk Drugs

There is, in effect, little or no FDA control of bulk drugs coming into this country, and there is currently no on-going enforcement action to serve as a meaningful deterrence to the trafficking and use of counterfeit or unapproved bulk drugs.

FDA inspectors at ports of entry do not have any information readily accessible that can be used to determine the authenticity of a particular drug, or whether a particular drug is an "FDA approved" bulk drug, or have access to information that identifies which U.S. drug manufacturers can legally use the bulk drug to make finished human drugs. Each U.S. manufacturer of prescription drugs can use only the bulk active ingredients which are articulated in an approved NDA/ANDA.

The only information made readily available to FDA inspectors at ports of entry to determine admissibility of bulk drugs is FDA Drug Listing. Drug listing is a requirement of 21 CFR Part 207, Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution. Drug listing has nothing to do with an FDA review to determine efficacy and safety. It is merely a mechanism for the Agency to monitor drugs in distribution by drug type and dosage forms. Anyone can obtain drug listing. In fact, Flavine has drug listings, as do other foreign and domestic firms who do not hold approved NDA/ANDA's.

If FDA inspectors find that the drugs in a shipment offered for importation are not drug listed, the shipment is administratively detained. Typically in response to the detention, the importer of record or their agent submits a drug registration/listing form to CDER. As long as the forms are completed satisfactorily, CDER provides notice the drugs are listed. The detained shipment is then released by FDA and allowed to proceed into U.S. commerce.

FDA's traditional manner of checking a finished drug manufacturer's system of handling raw materials during GMP inspections is not done in a manner that would likely detect the presence of counterfeit or unapproved bulk drugs. Typically the CSO randomly selects one shipment of one drug to determine if the firm's paper system covers the receipt, quarantine, and release of the bulk material and to determine the traceability of a specific lot of bulk drug to a lot(s) of finished dosage form. The issue of authenticity of the bulk drug is not directly approached.

The finished drug manufacturer's practice of determining the acceptability of a bulk drug relies predominantly with identity testing and information contained on certificates of analysis (COA's) provided to the firm by the supplier of that particular drug (See 21 CFR Part 211-Subpart E). Compendia identity testing is not likely to detect counterfeits or unapproved drugs unless some suspicious physical characteristic is observed, i.e., variance in color, odor, and granulation, etc.

It is common practice that the finished drug manufacturer accepts facsimile transmissions of COA's from the U.S. based supplier rather than have any direct communication from the actual or purported foreign manufacturer of the bulk drug. Often the COA's are on the supplier's letterhead rather than that of the bulk drug manufacturer. If the U.S. manufacturer questions a COA or has a problem with the imported bulk drug, it directs it's questions to the supplier for resolution. In the matter of counterfeits or unapproved drugs, it is likely the supplier is the counterfeiter, or at least the supplier knows the drugs are counterfeit or unapproved. FDA's traditional method of conducting GMP inspections of finished drug manufacturers does not directly approach the issue of authenticity of COA's.

Traditionally, FDA /ORA components do not communicate directly with foreign manufacturers of bulk drugs. Communications, including those made to arrange foreign inspection schedules, are made through the foreign company's U.S. representative or agent. FDA has relied on the U.S. company representative or agent to convey all pertinent information to the foreign manufacturer and to respond to the FDA on behalf of the foreign firm. So, if problems with bulk drugs made overseas were reported to FDA, then historically FDA would first communicate with the U.S. agent rather than communicate directly with the foreign firm. Flavine International was such an agent.

Conclusions and Recommendations

The Flavine International case has confirmed the threat to the human drug supply and public health posed by the international drug trade. Flavine is just one of several firms found by FDA/USCS to have handled counterfeit bulk drugs in 1991-1992. The importers of bulk generic drugs often supply both the veterinary and human drug industry. The character of the national/international drug trade is one in which everyone knows everybody else; individuals frequently move from one company to the other; and the drug traders are in position to control information between the FDA and the foreign bulk drug manufacturers.

The U.S. supply of foreign-made generic bulk drugs is controlled by a relatively small number of U.S. firms. There is a large global black or gray market of bulk drugs supplied by the Far East, Eastern Europe, and South America. The incentive to export drugs to the United States is money-- drugs exported to the U.S. can typically demand the highest price in the world. A bulk drug sold to the U.S. market may demand a price 100% greater than any other market, even if it's the same drug (as determined by identity and compendia tests) .

The same imported generic bulk antibiotic often can be used in the production of either human drugs or animal drugs. There is opportunity for importers to declare to FDA and USCS that a bulk drug is for veterinary use only, when in fact that is not the intended market. Once the shipment is released into U.S. commerce, the drug can be diverted to the human drug industry with little risk from FDA.

The investigation of imported counterfeit bulk drugs has disclosed many weaknesses in FDA's procedures which need to be conveyed by OCI via chain of command for correction. Most corrections will require action by or authorization from upper management. Joint effort will be required among various ORA components, including OCI, and CDER, to develop and implement effective enforcement procedures . OCI can provide recommendations that can be considered by the regulatory-side of the Agency. For example, OCI can recommend that GMP inspections of finished drug manufacturers routinely include audits of COA's and examinations of warehouse stocks of bulk drugs to determine authenticity.

Additionally, U.S. drug manufacturers need to be encouraged to do what is reasonable to ensure authenticity of goods received. FDA should encourage or require that the U.S. manufacturer, with little exception, accept only bulk drugs that are accompanied by original certificates of analysis (COA's). FDA should also encourage the U.S. firms to communicate directly with the foreign manufacturers to resolve problems.

OCI should also encourage changes in FDA import operations that would help deter and detect trafficking of counterfeit drugs. For example, OCI should recommend that evidence of authenticity, the NDA/ANDA or ANADA/NADA status of a drug, and the identification of the ultimate consignee should be the primary factors for determining admissibility. Drug listing needs to be discontinued as the primary criteria for determining admissibility of a drug shipment at the port of entry. Drug listing means nothing as far as FDA approval or compliance with any other FDA requirement. Drug listing, though, is a good source of intelligence for use in investigations.

OCI should also encourage FDA to routinely communicate directly with foreign drug manufacturers rather than rely on the purported U.S. agents to be the conduits. The U.S. agents are likely to be the primary subject of investigation when counterfeits or unapproved drugs are found. Using the U.S. agents as the primary network for communication to the foreign firms is like using a drug lord to pass information to the Columbian government. The international nature of the drug trade should support an ORA/ OCI request for a permanent presence overseas to ensure effective enforcement and provide meaningful deterrence of criminal activities.

The extent of the problem of imported counterfeit bulk drugs is not known. But we do know that the same regulatory and enforcement environment exists today that allowed Flavine to conduct counterfeiting activities for years with little risk. One might say that since no new cases have been developed since Flavine, there must not be a problem. However, the reality is that there is no procedure in place likely to detect the importation or use of counterfeit and unapproved bulk drugs in the manufacture of human drugs.

One must take a pro-active approach in assessing the real threat of imported bulk drugs and in developing other criminal cases. To that end I request permission to investigate the national and international problem of counterfeit human bulk drugs by being allowed to work pro-actively with FCC and USCS SSA The nature of the drug trade business, one in which every one knows every one else, lends itself to a centralized investigation. SSA and I know the most about the bulk drug problem for both USCS and FDA, and our combined expertise has the greatest chance for success.

SSA , who has been the only investigative continuity in counterfeit investigations since February, 1992, has the greatest institutional knowledge and expertise for USCS in the matter of counterfeit bulk drugs. He can readily obtain all information needed from USCS to develop new cases of counterfeit human bulk drugs, and can send domestic and foreign leads from the Kansas City RA Office as needed. Garrison is the only agent in USCS that knows the international drug trade that supplies bulk drugs to the U.S. and has a working knowledge of FDA drug requirements and procedures.

FCC has immediate access to much of the CDER information needed for successful case work. Besides traditional forensic/technical support, FCC has resources that can be mobilized to assist OCI in field work, i.e., execution of search warrants with large quantity of bulk drugs on the premises, collection of samples, etc. FCC needs guidance in its search for counterfeit and unapproved drugs. Investigation is required to find the counterfeits, not just forensic analysis. By virtue of its nature, a counterfeit is a result of intentional conduct. It is not a random event. A counterfeit can be found by conventional investigative techniques and then confirmed by forensic analysis. In the matter of oxytetracycline, it took 2 years after USCS seizures to forensically confirm the counterfeit status. FCC is not staffed appropriately to conduct independent investigations, but is staffed well to be an important member of a team charged with the mission to safeguard the public and ethical pharmaceutical industry from counterfeits.

I recommend that MWFO be the designated office for directing, conducting, and coordinating investigations of the national/international problem of counterfeit imported bulk drugs and that separate funding be considered so that other MWFO operations are not adversely impacted. I also recommend that MWFO be identified to other FDA components as the primary OCI contact in matters of imported counterfeit and unapproved bulk drugs. This is not an attempt to supplant OCI's Kansas City SAIC office's current role in the Flavine case. Direct spin-off cases from Flavine will be few and short-term since most counterfeiting activities that can be prosecuted will be running against the statute of limitations. Admissions by Flavine officials relative to counterfeit human bulk drugs demands quick action by the Agency to ensure the U.S. drug supply is reasonably safe from counterfeits, and MWFO is in the best position to do so.

Most U.S. manufacturers of human generic drugs are located along the east coast. The greatest volume of generic bulk drugs can be expected to be imported at ports along the east coast, or to be ultimately delivered to drug firms along the east coast. The greatest likelihood of venue for prosecution of any future counterfeit human bulk drug case is in the Mid-Atlantic and/or New York regions, but other federal jurisdictions can not be ruled out. Imported shipments of counterfeit or unapproved bulk drugs can be split and distributed to multiple end-users spread throughout the United States. Any federal jurisdiction with a port of entry (air, land or sea) has venue potential. Development of knowledge or intent requires investigation of the entire chain of distribution, from the foreign drug manufacturer to the U.S. finished drug manufacturer.

The legal and scientific issues related to national/international counterfeit bulk drug investigations is very complex. The best chance for success is for the Agency to allow a team possessing the greatest expertise to attack the problem, and allow the team to go wherever the investigation dictates it needs to go to be successful. An army is not needed to be effective. Development of a small cadre of "experts" is all that is needed. Initially, the only human resources needed are USCS SSA . FCC, and I. Resources would need to be reassessed if more counterfeits are found. If the bulk drug problem is found to be widespread, the counterfeit team can spin-off a case to the appropriate SAIC office and keep moving on the trail while it is hot. It is important to centralize information with the team in order to develop effective investigative strategies that will result in evidence that meets the burden of intent or knowledge. DOJ/OCL, who understands the counterfeit problem, can coordinate DOJ activities if multiple, concurrent cases occur.

The first task, though, is to determine whether counterfeits is an on-going problem, and, if so, to find and prosecute counterfeit cases. If investigation finds there is no significant imported bulk drug problem, then the work done to reach that conclusion can be used by the Agency to ensure the public and body politic that the generic drug supply is as safe as reasonably can be expected; and, OCI will have provided the leadership and necessary information to other Agency components to take appropriate action to implement an effective enforcement plan.

Carl Nielsen

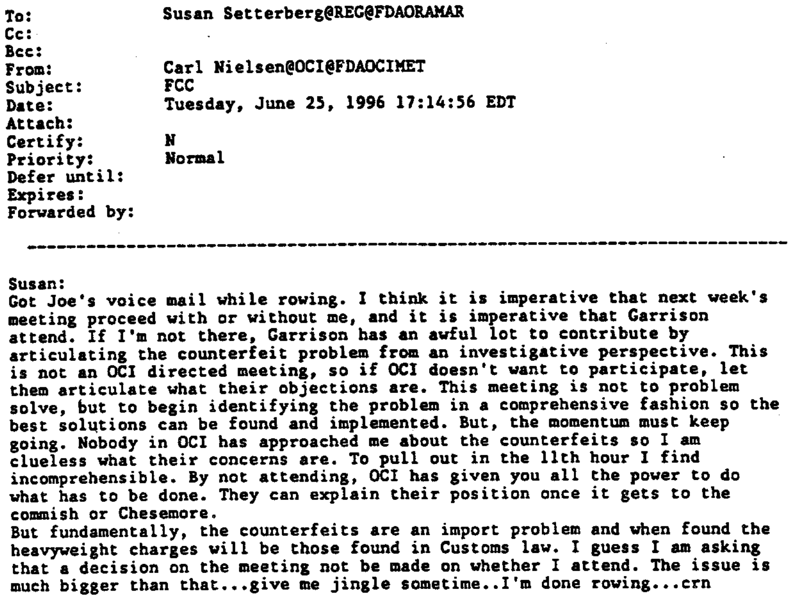
To: Fred Fricke@FCC@FDAORAMAR
Cc: Susan Setterberg@REG@FDAORAMAR
Bcc:
From: Carl Nielsen@OCI@FDAOCIMET
Subject: re: re: bulk drug initiative
Date: Wednesday, November 15, 1995 15:21:41 EST
Attach:
Certify: N
Forwarded by:

Fred-
I ditto everything you said. One correction is that we started working on counterfeit bulk drugs in June 1991 (1st seizure with US Customs in Baltimore). Garrison came on the scene in Feb 1992 after our investigation indicated there was tons of counterfeits at a firm in Kansas City and Iowa. As things have turned out, US Customs Agent Garrison has been the only continuity in the counterfeit bulk drug problem (except, of course, NFCC) since the problem was found in 1991. He's probably the foremost authority in the field.

Typical FDA drug programs, i.e., random sampling of bulks for compendial compliance, will, in all likelihood, not disclose the counterfeit nature of a product. So, the question begs, if it meets USP, what's the problem? The counterfeits we have found, indeed, consists of the actual active ingredient, but were made at unknown locations under unknown conditions, or at least, were made by a firm other than that which was claimed in the labeling. In order to sell the counterfeits, the bad guys know the victim finished dose manufacturer will at least check the incoming goods for identity testing. So we have not seen corn starch being substituted for gentamicin, as an example.

If the agency position would be, that the use of unapproved bulk drugs in the manufacture of NDA supported finished drugs poses no jeopardy to the quality and effectiveness of the finished dosage form, than we can afford to do nothing about counterfeits or unapproved bulk drugs. On the other hand, if the use of unapproved/counterfeit bulk drugs in the manufacture finished drugs does indeed invalidate the manufacturing process and thereby poses a real threat to the safety and efficacy of the finished drug, then we have a huge potential public safety problem. Any initiative put forward to remedy the problem must be focused on ensuring a USA drug supply free from counterfeit/unapproved bulk drugs. Sampling at the docks will not tell you if the product is authentic, nor does it ensure an authentic bulk drug will be used by a particular domestic manufacturer in a validated process specified by an approved NDA, etc. Sampling at the docks will tell you whether compendia is met, nothing else. The use of counterfeits and unapproved bulk drugs is a different problem. And if it is not a problem, then any finished drug manufacturer should be able to use any bulk active ingredient it can buy, regardless of who made it and where, as long as it meets compendial testing. And industry would really be happy if such an operation could be legal and supported scientifically, because unapproved/counterfeit bulk drugs on the world black market are half the cost of FDA approved drugs.

That's all I have to say...Carl



To: Susan Setterberg@REG@FDAORAMAR
Cc:
Bcc:
From: Carl Nielsen@OCI@FDAOCIMET
Subject: FCC
Date: Tuesday, June 25, 1996 17:14:56 EDT
Attach:
Certify: N
Priority: Normal
Defer until:
Expires:
Forwarded by:

Susan:
Got Joe's voice mail while rowing. I think it is imperative that next week's meeting proceed with or without me, and it is imperative that Garrison attend. If I'm not there, Garrison has an awful lot to contribute by articulating the counterfeit problem from an investigative perspective. This is not an OCI directed meeting, so if OCI doesn't want to participate, let them articulate what their objections are. This meeting is not to problem solve, but to begin identifying the problem in a comprehensive fashion so the best solutions can be found and implemented. But, the momentum must keep going. Nobody in OCI has approached me about the counterfeits so I am clueless what their concerns are. To pull out in the 11th hour I find incomprehensible. By not attending, OCI has given you all the power to do what has to be done. They can explain their position once it gets to the commish or Chesemore.
But fundamentally, the counterfeits are an import problem and when found the heavyweight charges will be those found in Customs law. I guess I am asking that a decision on the meeting not be made on whether I attend. The issue is much bigger than that...give me jingle sometime..I'm done rowing...crn

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
BALTIMORE DISTRICT OFFICE

MEMORANDUM

DATE: November 29, 1991

FROM: Director, Baltimore District, HFR-MA200

SUBJ: Importation of Counterfeit Bulk Drugs

TO: Gerald E. Vince, HFC-100

Baltimore District, in conjunction with U.S. Customs, is conducting an investigation relative to the importation of counterfeit bulk drugs. The cooperation between the agencies in this endeavor has been exemplary.

Information obtained by the investigators/agents suggests widespread availability of counterfeit bulk drugs in both human and animal drug industries. Assistant U.S. Attorney Gary Jordan of the Baltimore Generic Drug Task Force has been advised of the evidentiary potential as it relates to the generic drug industry.

Because of the potential impact of the on-going investigation on foreign travel, policies and resources of both U.S. Customs and FDA, I recommend the FDA investigators and U.S. Customs agents involved with the investigation give a presentation on the status to headquarter officials of both agencies. I suggest representatives from the following offices be included for attendance:

ORA - Mr. Ron Chesemore
Mr. Al Hoeting
Mr. W. M. Rogers, HFR-SW300
Mr. Michael Spangenberg, CSO, Omaha Resident Post

OGC - Mr. Eric Blumberg
Mr. Michael Petty

CVM - Dr. Gerald Guest
Mr. Ed Ballitch
Ms. Judy Gushee

CDER - Mr. Dan Michels

ORO - Ms. Mary Ayling
Mr. Joe McCallion
Mr. Bob Fish
Mr. Peter Smith

CIN-DO - Mr. Fred Fricke

If you concur, please extend an invitation to these individuals or revise the list as you believe appropriate.

It is very important appropriate representatives from U.S. Customs headquarters also be present since this investigation represents a "classic white-collar crime case" in which FDA 1811 agents will interact with U.S. Customs. Besides headquarter liaison officials, I recommend an invitation be extended to officials from U.S. Customs offices of Foreign Investigations, Commercial Fraud Enforcement and Domestic Operations. Additionally, we request that, through IOB's official U.S. Customs liaison, invitations be extended to Mr. Al Frare, Supervisor, Fraud Division, and Mr. Sam Neglia, Special Agent, U.S. Customs, Newark, NJ, to assist with the presentation. Both are knowledgeable of the facts.

I understand Import Operations Branch has made tentative arrangements for the presentation to be held in the ORA conference room, Thursday, December 12, 1991, from 11:30 am to 1:30 pm. This would be very satisfactory. I will be accompanied by Carl Nielsen, SCSO, and Benjamin England, CSO.

Thomas L Hooker
THOMAS L. HOOKER
District Director

cc: HFR-MA1
HFR-MA240
HFR-MA250

11/29/91: TLH/jjy

Volume 12, No. 6, 1998 International Pharmacy Journal

EDITORIAL

Counterfeit medicines

The dangers of counterfeit medicines were discussed for the first time at a FIP Congress in a symposium organised by the Section of Official Laboratories and a report appears in this issue. It was concluded that, although the problems in developed countries differ from the ones encountered in developing countries, the issue is a world-wide problem and no one is spared. Counterfeiting of medicines is not a new problem, but in developed countries it does not receive much publicity. Only the detection of counterfeit Zantac in Europe a few years ago became more widely known.

What is the attraction of counterfeit medicines for criminals? There are three basic explanations. They are difficult to detect; a small consignment may have a huge market value; current legislative provisions make traffic in them safer than in hard drugs. The first time that the issue was raised at WHO level was at the Nairobi Conference of Experts on the Rational Use of Drugs in 1985, and it was taken up again in a resolution adopted by the World Health Assembly in 1988. Since then, two international meetings co-sponsored by WHO and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) have been organised. These have highlighted the importance of a tight distribution chain and have resulted in formal WHO guidance on the inspection of the distribution channel which is to be published shortly. There is much evidence to show that where regulation is less effective, counterfeit products become more prevalent and less sophisticated. It is clear that the populations of developing countries are at greatest risk, particularly where medicines are available not only from regulated pharmacies but also from street hawkers. However, a recent investigation in Nigeria reported in this issue demonstrates that even products dispensed from pharmacies can be counterfeit. In developing countries products labelled as antimalarials and antibiotics often contain little or nothing of the declared active ingredients and, apart from the disastrous effect on treated patients and the undermining of confidence in the health systems, such products can promote the emergence of microbial resistance to antibiotics.

Counterfeiting is not limited to finished products, it may also extend to starting materials. At a seminar of inspectors organised by the Pharmaceutical Inspection Convention (PIC) in 1997, it was reported that two countries had detected imports of counterfeited active ingredients. These two countries are exceptional in having criminal investigation units working together with the drug regulatory authorities. It is reasonable to speculate that only the tip of the iceberg has been sighted and that a far more profound problem exists.

What can be done? The best way to reduce the circulation of counterfeit medicines is strict compliance with GMP at the manufacturing stage and utmost vigilance by everybody. Only a tight distribution chain where every handler of these products is licensed, obliged to keep precise records, and regularly inspected will satisfy these needs. It is relevant to note that, with the abolishment of import controls between the countries of the European Union, emphasis has been shifted to the inspection of the distribution channels.

Over the years WHO has tried to collect information on the detection of counterfeit products but little of this information comes from the manufactures themselves. In general, the multinational companies try to deal with the matter themselves. The following policy statement on counterfeit products issued by a major multinational company via the Internet, demonstrates how they tackle the problem: any counterfeiting of their products is thoroughly and promptly investigated. The products are designed to incorporate features which make them difficult to copy and which facilitate counterfeit detection. Effective control is exercised over the production and use of product components and packaging materials, and over the disposal of samples and materials rejected during the production process. The level of counterfeiting in the local markets and the effectiveness of the counter-measures used are kept under continuous review. While the company will continue to do whatever it can to make counterfeit products more difficult to produce and easier to detect, this will not prevent counterfeits from reaching the market. The company will therefore work in co-operation with pharmacists, wholesalers, government agencies, and other pharmaceutical companies to ensure that suspected counterfeiters and their intermediaries are thoroughly investigated and, where appropriate, prosecuted. The company will also work with IFPMA, WHO and other appropriate bodies to encourage action at national and international level to create an environment hostile to counterfeiting.

And what are the pharmacists to do? As the professionals with first hand responsibility for the medicines they buy and dispense, they are directly concerned. If they always procure their products from reliable suppliers and keep vigilant to detect any anomalies, the circulation of counterfeit products can be reduced to a minimum. As the international body representative of the profession, FIP should issue a policy statement on the matter.

A. Wehrli

Les contrefaçons

Les dangers que présentent les médicaments contrefaits ont été discutés pendant un Congrès de la FIP pour la première fois lors d'un symposium organisé par la Section des Laboratoires Officiels, dont le rapport est publié ailleurs dans ce Journal. La conclusion est que, bien que les problèmes dans les pays développés soient différents de ceux dans les pays en développement, la question est un problème mondial qui nous touche tous. La contrefaçon de médicaments n'est pas un problème nouveau, mais dans les pays développés cela n'est pas très connu. Seule la détection de

Quel attrait présente la contrefaçon de médicaments pour les criminels? Il y a trois explications fondamentales: ils sont difficiles à détecter; une petite quantité peut représenter une valeur énorme sur le marché et les dispositions législatives actuelles en rendent le trafic plus sûr que celui des stupéfiants. Cette question fut soulevée à l'OMS pour la première fois pendant la Conférence d'experts sur l'emploi rationnel des médicaments à Nairobi en 1985, et le problème fut repris dans une résolution adoptée par l'Assemblée Mondiale de la Santé en 1988. Depuis, deux réunions internationales

produits pharmaceutiques (IFPMA) ont été organisées. Elles ont souligné l'importance d'une chaîne de distribution hermétique et ont résulté dans une directive formelle de l'OMS sur l'inspection des canaux de distribution qui sera publiée sous peu. Il a été amplement prouvé que là où les réglementations ne sont pas très efficaces, les produits contrefaits deviennent plus prévalents et moins sophistiqués. Il est clair que les populations des pays en développement courent de grands risques, surtout là où les médicaments sont disponibles non seulement par les pharmacies contrôlées

PHARMACEUTICAL INSPECTION CONVENTION-PHARMACEUTICAL INSPECTION CONVENTION SCHEME

PIC-PIC/S Seminar 1997
10-12 June 1997, Naantali, Finland

Counterfeited and substandard active pharmaceutical ingredients

by

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Introduction

WHO was first alerted to the circulation of counterfeit pharmaceuticals at the Conference of experts on the rational use of drugs in Nairobi, in November 1985. Since then concern about the situation has been raised repeatedly by delegations at the World Health Assembly and this has been reflected in several resolutions. Resolution WHA41.16 adopted in May 1988 requested the Director-General *to initiate programmes for the prevention and detection of the export, import and smuggling of falsely labelled, spurious, counterfeited or substandard pharmaceutical preparations and to cooperate with the Secretary-General of the United Nations in such cases when the provisions of international drug treaties are violated.*

The Secretariat has retained these resolutions in mind throughout its efforts over the past decade to refine its norms and guidelines in a way that stimulates closer collaboration between regulatory authorities and in its exchange of information and training of drug regulators that it organizes in the less developed countries which are most vulnerable to these illicit activities.

In April 1992, WHO, together with the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), organized a special workshop on counterfeit drugs. It became evident that both developing and developed countries are confronted with counterfeit pharmaceuticals which range from highly sophisticated counterfeits of branded products which are almost indistinguishable from the authentic product, to potentially dangerous substandard or spurious preparations sold under branded or generic labels. Where there is strong regulation the infringements are fewer in number and highly sophisticated. Where the risk of detection is lower, so the infringements increase in number and the misrepresentations become more crude. WHO has created a data base containing more than 700 case reports collected over a period of 15 years. In the developing countries it is essential live saving drugs that are most commonly counterfeited, including antibiotics and antiparasitics. All reports other than widely publicised reports of trade in glycerol (glycerin) contaminated with diethylene glycol concern finished dosage forms.

The counterfeit issue was on the agenda of the last two International Conferences of National Drug Regulatory Authorities (ICDRA) held in The Netherlands and in Bahrain in 1994 (1) and in 1996 (2) respectively.

At the ICDRA in the Netherlands in 1994 Mr B. Hartley, UK reported evidence that a number of counterfeited APIs were in international circulation (1). Developing countries that have to import most or all of their APIs have been complaining for years about substandard APIs in international trade and this led WHO to propose in 1988 that the Certification Scheme be extended to the certification of APIs.

Definition of a counterfeit API

The 1992 WHO/IFPMA workshop report defines a *counterfeit medicine* as one which is *deliberately and fraudulently mislabelled with respect to identity and/or source*. If this definition is extended to APIs, this will underscore the need to establish their true origin and have it reflected on the label.

Because of the present lack of regulation of APIs it is unclear to what extent the definition of *manufacture*, and *manufacturer* as defined e.g. in the WHO/GMP text and in Article 16 of Directive 75/319/EEC referred to under *manufacturer* in the glossary in the EC/GMP, text are also applicable APIs. If they are, the opportunity arises for a company or an individual involved in "partial manufacture" - perhaps only repackaging - to place their name on the label without further reference to the manufacturer responsible for the chemical synthesis. Any relevant legal instrument must ban this practice by defining it as deliberate mislabelling with a view to obscuring the true provenance of the material.

The legal status of APIs differs fundamentally from that of finished dosage forms. APIs are not subject to a marketing authorization, although they are regulated indirectly through the Drug Master File (DMF). However, this applies only to highly developed countries and even there, their marketing, and often also labelling, are not regulated.

Finished dosage forms are subject to a marketing authorization, their labelling is strictly regulated and always requires display of the marketing authorization holder, even when he is not the manufacturer. While some countries have requirements to also display the name of the actual manufacturer, this is less important for dosage forms than for APIs since the drug regulatory authority can always trace the latter through the registration dossier.

Case reports

The following reports on counterfeit APIs have been provided upon specific request or identified in publications. Several of them illustrate the labelling problem:

Therapeutic Goods Administration, Australia (3):

The TGA made a communication to the PIC-PIC/S Committee of Officials in February 1997 stating that the practice of substitution of APIs appeared to be an increasing problem for APIs manufactured in, and supplied from, Asia. The examples they had evidence about include the following:

> Delivery to an Australian manufacture of sulfamethoxazole manufactured in India which had been partially substituted with sugar milled to the same particle size as the API. The substitution involved three of 10 containers in the delivery.
>
> Inferior grade APIs, including rejected APIs, are being placed at the bottom of drums in every 3rd or 4th drum in a delivery.
>
> Apparently these substitution rackets have access to sophisticated packaging technology (including access to "tamper-proof" security devices) and may even co-opt company employees (either the API manufacturer or the label printer) to provide packaging information or the security or packaging material itself. It seems that the actual substitution of material often takes place immediately after the consignment of API leaves the premises of the true manufacturer.

This information was circulated by the chairman of the PIC-PIC/S Committee, asking other inspectorates whether their countries noted similar problems, whether there was need to insist on "top, middle and bottom" sampling of each container of API received from specific Asian countries, and whether information about counterfeiting should be disseminated within PIC-PIC/S and shared with WHO, other inspectorates and industry. So far the PIC/S secretariat has not received any feedback. However, the TGA, has provided WHO with the following further examples they had investigated:

> An antibiotic substance exported from a country in Western Europe was actually manufactured in meso-America, then sent to the European parent company where it was repackaged, reanalyzed and issued with a new certificate of analysis before being shipped to Australia. The label

> and documentation gave the impression that the API originated from Europe and the Australian affiliate company was not informed about the true origin until the investigation clarified the origin.
>
> A low volume orphan drug API documented as originating from a Western European country, was actually produced in a country in Eastern Europe. The practice went undetected by the Australian affiliate company for about a decade until the Western European plant was dismantled. Then the parent company admitted to the affiliate what had been happening.
>
> The Western European companies were even prepared to argue that the value added nature of the work conducted in Europe was greater than 50% of the cost of the API sold to Australia and hence were entitled to claim that it was "made" in that particular European country.

No action could be taken in these instances. The Australian companies had not committed any offence and no prosecution of the overseas companies in Australia was possible. But, in any case, it is unlikely, because of lack of regulation of production (Whether *de novo* synthesis or merely repacking of the API and exports of APIs, that the authorities in the exporting country would have had any basis for legal intervention.

The TGA is aware of other anecdotal stories about substitution, dilution or adulteration. These include: mixing subpotent material with normal material in such a way as to just pass the pharmacopoeial specifications; substitution of technical grade for pharmaceutical grade. However, the TGA has no firm evidence of such cases.

Office of Criminal Investigation, FDA, USA(4):

The following information has been received from the US FDA, Office of Criminal Investigation regarding recent cases involving APIs. The investigation was worked jointly with the U.S. Customs Service:

> In 1991 chemists at SmithKline Beecham Laboratories notified the FDA of counterfeit *oxytetracycline* at their Animal Health Facility, Omaha, Nebraska. Investigation uncovered a conspiracy to import and distribute counterfeit bulk drugs. In 1996, Flavine International Inc. and three individuals were fined on account of conspiracy to commit drug counterfeiting and to commit money laundering. Flavine signed a plea agreement which settled a fine of §925.000 against charges of conspiracy and money laundering. One of the individuals was fined §75.000 and for 24 months imprisonment.
>
> The investigation determined that Flavine International Cooperation had employees who circumvented legitimate business practices on the grounds that the demand in the market place for certain drugs was greater than capacity of the business to satisfy. The circumvention thus increased their profit margin. National Drug Codes (NDC) were "Switched" and Counterfeit Certificates of Analysis (COAs) were produced, reflecting the false NDC codes, false manufacturers and false batch code information. In essence legitimate API was replaced with counterfeit API, or repackaged into drums that the legitimate manufacturer did not utilize. In all instances the legitimate drug was replaced with a drug which purported to be the approved U.S. API, when in fact it was not.
>
> Legitimate firms that received the counterfeit products did not challenge Flavine when they observed unusual sized and mismatched drums containing the same drug.

The drugs that were affected by Flavine's business practice were: chlortetracycline, oxytetracycline base, tetracyline, chlorampheniol, gentamicin, neomycin sulfate, sulfamethazine, and methyldopa.

Medicines Control Agency, UK:

The examples of completed cases and on which information could be provided involve all pharmaceutical products and not substances. However, the way in which they were handled could equally apply to APIs. The examples given are as follows:

- A licensed UK wholesale distributor was found to have stocks of pharmaceutical products in premises other than those premises declared on the licence. These products were imports for which the company did not have marketing authorizations. The products had been removed from original containers and re-packaged to disguise origin and expiry dates were extended beyond shelf-life. The licence was withdrawn and the company and its owner successfully prosecuted.

- An unlicensed trader was found to import large quantities of pharmaceutical products from outside the European Community, manufactured on unlicensed sites and selling stock to pharmacies "from the back of his van". Surveillance was used to investigate his activities. He was arrested, his stock seized and the proceeds from his sales seized. He was successfully prosecuted as was an accomplice. The pharmacists to whom he sold were reported to their professional association.

- A licensed wholesaler who substituted batch numbers on a substantial quantity of stock he was not licensed to sell was successfully prosecuted.

The following cases still under investigation in the UK involve: illicit manufacture; obtaining actives from unlicensed sites in the Far East; assembling products and passing them off as the licensed product; assembly and passing off as genuine in the UK a product containing only half the API; and so on.

The counterfeited product in the UK tends to be a prescription only medicine and one for which either demand and sale price are high, or for which there is a specialist market prepared to pay a high price.
Prosecutions generally result in fines, occasionally a prison sentence. However, UK legislation permits sequestration of assets gained by unlawful activity and the MCA can request courts to confiscate property, money and other assets. The consignments of pharmaceutical products are also seized. These actions are intended to make counterfeiting activities unrewarding and as a deterrent can be more effective than fine or even imprisonment.

Pharmaceutical Security Institute (PIS), IFPMA

The PIS is funded by the majority of ethical pharmaceutical companies and operates under the auspices of the International Pharmaceutical Manufacturers Association (IFPMA). The functions of the institute include: supervision of enquiries, world-wide, into unlawful acts against the ethical pharmaceutical industry - counterfeiting in particular - and liaison with law-enforcement agencies, particularly police and customs officials, to combat these unlawful acts and bring the perpetrators to justice.

The ethical industry is well aware of the problem posed by the counterfeiting of APIs and is taking steps to deal with it. A number of cases are currently under investigation and the results of those investigations will be handed over to the competent authorities on their completion. The PSI, which is co-ordinating these investigations, also confirms that such cases are not confined, geographically to one region, and that counterfeit APIs are being manufactured in, and sold through, a number of different countries.
An API may be counterfeited in one country, passed by a circuitous route into another for formulation; from there to a third country where the product is sold. Often the finished product transits several more countries before it reaches its final destination. To add further confusion, investigation has shown that, in a number of cases, bulk pharmaceutical containers are switched so as to present the appearance of a given substance emanating from a European

country when, in fact, it may have originated from the Far East. This activity poses a particular problem for both law-enforcement and national regulatory agencies, as it becomes extremely difficult to pin down which authority has jurisdiction in any given case.

Published Reports:

SCRIP No 2189 December 13th 1996 p.16:
PhRMA refers to several of its members having recently experienced counterfeiting of their top-selling prescription products and cites as a case that "can be affirmed as having been proven" a counterfeit API produced in and exported from China. The API often reaches countries in which the innovator companies hold enforceable patents, and in many cases, the Chinese APIs are shipped to Hong Kong, repackaged, and shipped on to other markets, often in the developed world, where they are marketed as the patent holder's product.

Marketletter, April 21, 1997, p.16:
Refers to the fact that currently Pakistan depends entirely on imports for its basic raw materials, the cheapest source being China. According to industry believes Indian-manufactured basic APIs worth $2 million come to Pakistan through Hong Kong, Singapore, Dubai and Europe under other-than-India country of origin labels, and the new government aims to reduce this trade.

Repackaging and relabelling with the name of the repackager is the common denominator in most of these reports. The question is whether the practices could really be considered as illegal in all cases, in particular in the case of the two Australian examples where APIs were reanalyzed and repackaged in Western Europe.

Contamination of glycerol (glycerine) and propyleneglycol with diethylene glycol

Experience with these two solvents indicates that safeguards need to be applied to all materials included in formulated dosage forms and not just APIs. Contamination or substitution with diethylene glycol in the manufacture of pharmaceutical products has resulted in deaths of over 500 patients in Argentina, Bangladesh, India, Nigeria and Haiti in recent years. WHO sent warnings to drug regulatory authorities in all Member States after the Bangladesh incident in 1992 and also after the recent Haiti incident in 1996.

Over 80 children died in the Haiti incident last summer and the case has been investigated by the Haitian health ministry with help of the US Food and Drug Administration (FDA), the US Centre for Disease Control and Prevention (CDC) and WHO/PAHO. These parties also organized a special workshop on diethylene glycol contamination in Washington D.C. in February 1997. The outcome of the meeting will be a report about the overall diethylene glycol problem with recommendations on how to prevent the problem in the future. It will also contain simple analytical test procedures that allow the detection of down to 0.2% content of diethylene glycol.

WHO has received extensive material prepared by the Freedom of information staff of FDA's Center for Drug Evaluation and Research for disclosure to public requesters (5). The material demonstrates the risks involved in procuring APIs through free zones and brokers.

It is thus of interest to have a closer look at this case history extracted from the US material.

The manufacturer of the liquid used to prepare the deadly syrup is still unknown. The material was originally shipped from Xiangang (China) via the free port in Rotterdam (Netherlands) to Port au Prince. The commercial transactions involved the following:

Sinochem International Chemicals
Beijing, China

Metall-Chemie Handelsgesellschaft m.b.H. & LTD.
Hamburg, Germany

Vos B.V. (subsidiary company of Helm AG Germany)
Alphen a/d Rijn, Netherlands

Chemical Trading and Consulting Company GmbH. (CTC)
Reinfeld, Germany

Pharval Laboratories
Port au Prince, Haiti

The three European parties involved never saw the merchandise, not even Vos B.V. to whom the mercahndise was sent from China. Vos B.V. merely gave instructions to the people in charge of the rented commercial warehouse at the Rotterdam port.

When the material arrived in the Rotterdam warehouse the only labelling on the drums consisted of white stenciled markings as:

"GLYCERINE 1.26**4962/1-UP**GROSS WEIGHT: 260 KG
NET WEIGHT: 260 KGROTTERDAM

The 1.6 refers to specific gravity and the 1-UP means shipment contains more than one drum, in this case 1 drum up to 72 drums. 4962 represents the Vos purchase number.

The following black stenciled marking were added upon instructions from Vos B.V.:

"GLYCERINE98 PCT USP**4962/01**NET 260 KOS**GROSS CA 260 KOS"

According to the records, the Vos B.V. employees mentioned that laxity over labelling of drums was widespread for import-export business. For shipment within Europe labelling of containers is highly regulated and Vos B.V. must print labels themselves, including all the hazardous statements that apply to the chemical. Otherwise, the materials are commonly transported with little identification. Everything is dependent upon dissociated paperwork.

Vos B.V. provided records of the movement of two shipments which go back to China Ocean Shipping Co.. In these records the following names are used::

Glycerin USP 21"pharma grade"

Synthetic glycerin USP 21

Glycerine USP

The records include an undated/unsigned certificate of analysis (COA) for Glycerine USP in English with Asian characters supplied under the name of Metall-Chemie on which it is mentioned "datas as received from our supplier". Metall-Chemie confirmed that the certificate supplied is a photocopy where the heading with the name of Sinochem has been covered by their own name.

It has been shown that throughout these complex transactions vital information on the provenance and the nature of the material was deliberately obliterated on documents and product containers, a practice traders commonly use to protect their business interests and refer to as "neutralization".

Pharval Laboratories, the pharmaceutical manufacturer in Haiti used the product traded in this way for the preparation of paracetamol oral syrups and oral drops for neonates. After the incident the manufacturer was visited by an FDA inspector and found to be in gross violation with basic GMP principles. Thus, the incoming starting materials were not being tested, certificates of analyses were not always available, and no in-process quality control and final product testing was implemented etc.

The factory has been closed and the matter is before the courts in Haiti where bereaved families are claiming compensation. According to an article published in the Netherlands by NRC Handelsblad and reproduced in English in the World Press Review in May 1997, Pharval mentioned that they imported a great deal of material from Germany to be certain of its quality. It was CTC however who sold them the adulterated glycerin. Pharval also mentioned that had they wanted a Chinese product then they would have imported it directly from there. The price Pharval paid was practically twice the price Vos B.V. paid for it in China.

Strategies for combating trade in counterfeited and substandard APIs

Comprehensive and effective drug regulatory systems, including rigorous pharmaceutical inspection of facilities, where APIs and dosage forms are manufactured and closer oversight of wholesalers, brokers and other traders - also in free ports - must be in place if the above illustrated incidents are to be averted in the future. Some countries already require that manufacture of APIs is undertaken in accordance with GMP and a few undertake inspections on a statutory or voluntary basis.

The following decisions or ongoing discussion are new important elements of relevance to these strategies:

International working group on GMP for APIs convened under the aegis of PIC-PIC/S

A progress report on the work of this group has been presented on the first day of this seminar.

World Health Organization:

In 1988 the World Health Assembly extended the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce to starting materials for use in pharmaceutical dosage forms *when it is subject to legislation in the exporting Member state and in the importing Member State*. This was followed by publication of a WHO guide on GMP for APIs (practically identical to the corresponding PIC text) in 1992 (6). A first draft guideline on the certification of APIs was presented at the PIC-PIC/S Conference on the GMP for APIs in Canberra last September and a proposal will have to be submitted to the World Health Assembly in the year 2000.
The draft guidelines specifically address labelling and certificates of analysis. During its Thirty-fifth meeting, the Expert Committee on Specifications for Pharmaceutical Preparations also adopted a GMP text for pharmaceutical excipients.

European Pharmacopoeia (EP)

The European Pharmacopoeia introduced a system referred to as *Certification of suitability of the monographs of the PH.EUR* in 1992. This system affirms that a given substance from an identified source can be suitably analyzed in accordance with the respective EP monograph. It is based on evaluation of samples and Drug Master Files (DMFs), but, for the time being, is not linked to inspection of the manufacturing site. The list of certificates of suitability is regularly updated and published in Pharmeuropa, The European Pharmacopoeia Forum.

European Community:

The EC has issued the following EC directive and corresponding guidelines for its implementation;
- Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use
- Guidelines on good distribution practice of medicinal products for human use (94/C 63/03, text with EEA relevance)

The *Guidelines* contain specific sections on *record keeping* and also on *counterfeit medicinal products*, but they do not specifically apply to APIs.

The EC is revising the Directive 75/319/EEC in order also to address regulation of APIs and critical excipients. A guideline for implementation of the revised Directive is also anticipated.

North American Free Trade Agreement (NAFTA)

Annex 311 of the North American Free Trade Agreement (NAFTA) entitled *Country of Origin Marking* requires that the country of origin of imported active ingredients be displayed on the label of finished pharmaceutical products when these ingredients comprise 60% or more of the final weight of the product. The implication is that regulations on the labelling of APIs will require strengthening to ensure that the identity of the original manufacturer is never concealed.

The reference to this was found in an Indian periodical, The Eastern Pharmacist (7).

Pharmaceutical Industry

The pharmaceutical industry has recently created the *Pharmaceutical Security Institute (PSI)* referred to under the case reports section.

Conclusions and recommendations:

There is evidence of international trade in counterfeited and substandard APIs and other starting materials used in the manufacture of medicines. The magnitude of this trade is unknown but it is certainly far greater than is evident from the case histories that have filtered through into the public domain. Most problems have been found in countries that have exerted themselves to investigate the situation. The range of illicit activities, even in highly regulated countries, provides some most telling evidence yet available that countermeasures are needed and that this needs to be coordinated on a global basis.

The Haiti case provides a specific insight into the complexities and dangers of current trading practices in these materials. At least four traders (three of them in Europe) were interposed between the manufacturer of the starting material in China and the manufacturer of the dosage form in Haiti. On its way, the shipment passed through a European free port. Such complex movements coupled with lax - and often non-existant labelling regulations - simply serve to obscure the true origin of the products and they compound the danger of substitution and tampering. They also frustrate effective investigation of associated commercial activities in a situation where detection is already remote when - as in many small companies in less developed countries - there is little chance that substances will be analyzed by the end user. Public safety is promoted when bulk materials are purchased directly from the manufacturer, or, failing this, from an intermediary nominated by the manufacturer.

The catalogue of repeated tragedies attributed to diethylene glycol poisoning should serve as an incentive for legal and regulatory initiatives to improve the safety of trade in pharmaceutical starting materials. In the meantime it should convince traders of the need to introduce a code of marketing on a voluntary basis.

The following recommendations are consonant with proposals that have emerged from various WHO meetings and conferences but some additional ideas are offered that are of particular relevance to APIs and other starting materials:

Drug regulatory authorities should:

- seek to extend their regulatory mandate to manufacturers of APIs particularly in relation to inspection for compliance with GMP, and rigorous requirements for labelling and certificates of analysis for consignments moving in international commerce
- seek to introduce regulations that require APIs and all other starting

materials intended for the formulation of medicinal products to be clearly labelled as being "For pharmaceutical use" or with a suitable pictogramme

- establish within the regulatory authority a multidisciplinary group to investigate illicit activities promptly and professionally

- monitor free ports more intensively and strengthen collaboration with law enforcement agencies including customs offices, and offices of criminal investigation, at both national and international level

- seek to enact legislation that permits sequestration of assets gained by unlawful activity and seizure and destruction of products involved in such activity

WHO should

- develop a network of technically-competent officials within national drug regulatory authorities with a view to ensuring timely exchange of information, both on cases of counterfeit and any countermeasures taken at national level

- act as a clearing house for exchange of information on counterfeit pharmaceuticals

- develop guidelines for the certification of API's moving in international commerce

Pharmaceutical manufacturers/wholesalers/traders should

- be cautious in procurement of APIs and finished products and in introducing products into the distribution channel

- maintain vigilance in detecting counterfeiting or substitution of dosage forms and APIs which they produce and distribute

- share information with regulatory authorities; this information should be handled with due discretion to avoid loss of confidence in genuine products

Manufacturers of finished dosage forms in particular, should:

- buy APIs whenever possible from the original manufacturer, or when through traders, insist on transparent and full documentation about origin and certificates of analysis

- be aware of their responsibility and liability for assessing and ensuring the quality of APIs and starting materials they use, and the rigorous conditions (outlined in GMP) to be applied in exceptional situations when reliance is vested in the supplier's certificate of analysis in place of a full re-analysis

To what extent all these recommendations are realistic remains to be discussed. The effect of additional laws and regulations depends on their implementation which implies increased inspection capacities requiring more resources. The final responsibility of the manufacturer using the API cannot be overstressed. He has to insist that the supplier informs him about the true origin of the API. Many small manufacturers in developing countries have little bargaining power to insist on this transparency and action needs to be considered with urgency.

References

(1) Seventh International Conference of Drug Regulatory Authorities, the Hague Netherlands 18-22 April 1994, page 10 (WHO/DMP/ICDRA/94.1),

(2) Eighth International Conference of Drug Regulatory Authorities, Manama,

Bahrain, 10-13 November 1996 (WHO/DMP/ICDRA/97.1)

(3) Note from the Therapeutics Goods Administration (TGA) entitled Substitution of Active Pharmaceutical Ingredients distributed during PIC-PIC/S meeting of officials in Geneva in February 1997; letters from TGA addressed to WHO on 3 and 25 March 1997

(4) Letters from the US FDA Office of Criminal Investigations addressed to WHO on 28 February and 7 April 1997

(5) Haiti report package as prepared by the Freedom of Information Staff of FDA's Center for Drug Evaluation and Research for disclosure to public interest, provided by the Office of International Affairs of the US Department of Health and Human Services on 20 February 1997

(6) WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second Report, WHO Technical Report Series No. 823, WHO Geneva, 1992 (p.72, section 18 of GMP for pharmaceutical products)

(7) The Eastern Pharmacist, an independent organ of the pharmaceutical industry, trade and profession, Vol.XL.No.469, January 1997, page 70-71 (Pamposan Publications, 506, Ashok Bhawan, 98, Nehru Place, New Delhi-110 019, India)

The following are abstracts of open source media reports that mention counterfeit pharmaceuticals and related crime. The dates range from November, 1998 to May, 2000. This list does not reference every media report on counterfeiting nor does it contain confidential or non-media information.

1. *(South China Morning Post, May 26, 2000)* Fake malaria medicines flooding the Cambodian market have killed dozens of people in the past year, and the Government has done little to stop it, officials said. The fake drugs - marketed as the powerful malaria medicines Mefloquine and Artesunate, but actually of no medicinal value - had accounted for the deaths of at least 30 people so far this year, according to Dr Duong Socheath, director of the National Centre for Combating Malaria. The fake medicines targeted the poor because they were cheaper than genuine remedies, said Jan Rozendaal, adviser to the European Commission's malaria control program. "Patients go for the cheaper one. They think they are saving money," he said. Among the most high-profile victims of the faux medicines was Sam Veasna, head of the Government's Wildlife Protection Office in the northwestern town of Siem Reap. He contracted malaria while conducting a survey and began taking Mefloquine, or so he thought. Instead of getting better, his symptoms worsened and he fell into a coma, dying within six days. Health professionals say they are shocked at the cynical trade in ineffective drugs, which they believe are being produced in a neighboring country and shipped to the Cambodian market.

2. *(Marketletter, May 22, 2000)* A lack of leadership at the US Food and Drug Administration and weakness in its import system has left the USA vulnerable to potentially counterfeit, substandard, contaminated or poisoned imports of bulk

drugs, House Commerce Committee chairman Tom Bliley has told FDA Commissioner Jane Henney. In a letter detailing nearly two years of investigations by the Committee, Rep Bliley says that the FDA "has little or no control of imported counterfeit bulks entering the USA, providing no meaningful deterrence to trafficking of these products." The letter details the case of imported gentamicin sulfate, particularly that supplied by Long March Pharmaceutical of China. From 1989 to August 16, 1994, the product was associated with 1,974 adverse events including 96 disabilities and 49 deaths. The FDA issued an import alert on Long March's product in September 1999, but FDA data show 254 adverse events associated with it from May 1, 1999, to January 11, 2000, including 202 serious events and 17 deaths. "I am concerned that Long March bulk drugs and/or counterfeit gentamicin sulfate from China may still be entering the US health care system," he says.

3. *(BBC Monitoring Central Asia Unit, May 20, 2000)* A large batch of out-of-date medicines illegally imported from abroad was burned in Uzbek. The medicines were illegally imported and are smuggled into the country. In general, they come by the Delhi-Tashkent route. Then they are distributed throughout the Regions and sold by chemists. Often these medicines are not suitable for their purposes. D.Nasyrova, head of pharmacological inspections said the counterfeit medicines are labeled as having been produced in Poland, India and Bulgaria. Government test showed the medicines were produced in India and did not have all the basic ingredients making the medicines useless. Six tons of illegally-imported medicines have been detained by customs officers over the last two years.

4. *(Africa News, May 19, 2000)* South African police and the Heath special investigating unit recently arrested a number

of suspects involved in the distribution of counterfeit and stolen medicine. Counterfeit, expired and stolen medicine to the value of R100m was confiscated.

5. *(Africa News, May 18, 2000)* A senior official from Benin's health ministry, has expressed concern at the growing utilisation of counterfeit drugs, particularly among poor countries. Dr Idrissou Abdoulaye told the ongoing session of the World Health Assembly in Geneva that poor people buy these dangerous drugs because they are cheap. "Every day people die because of counterfeit drugs," The criminals are running highly sophisticated operations taking advantage of cross-border loopholes. Supplies, production, shipping, re-labeling, financing, distribution are all handled in different countries.

6. *(Chemical News & Intelligence, May 18, 2000)* Pharmaceutical industry officials said they are seeking federal government action against a Mexican company they accuse of manufacturing counterfeit drugs and supplements. The executive director of the Association for Pharmaceutical Industry Investigations (AMIIF) filed a formal complaint with the federal Health Secretary alleging counterfeit drugs manufacturing and tax evasion by the single firm. The organization stated, "We have tested a number of these supposedly generic products currently on sale at pharmacies throughout the country and have found that are not what they claim to be and can cause damage to one's health." AMIIF warned that, according to its own independent testing, the substitute drugs are not chemically equal to the originals.

7. *(USA Today, May 9, 2000)* Citing information in "adverse event" reports the FDA received from doctors and others, [Representative] Bliley disclosed for the first time that 49 people may have died from 1989 through 1994 after

gentamicin injections. Bliley named China-based Long March Pharmaceutical as a problem manufacturer and exporter of bulk gentamicin. He says many adverse event reports have been linked to U.S. companies that have used supplies from Long March, including Fujisawa USA. A Fujisawa spokesman says the firm no longer makes the drug. The FDA issued an "import alert" last year banning Long March gentamicin from the USA. Evidence indicates that the firm's product "may still be entering the U.S," Bliley says. Long March didn't have an immediate comment, and the Chinese Embassy didn't return phone messages.

8. *(Deutsche Presse-Agentur, May 7, 2000)* A fake anti-obesity drug which looks like the real thing has been found on sale in Hong Kong. Counterfeit packets of the popular drug Xenical are being sold in pharmacies in the territory and a joint Department of Health and customs investigation has been launched.

9. *(The Plain Dealer, May 2, 2000)* A 62-year-old man surrendered to Boston Heights police yesterday on charges that he sold fake Propecia and phony Viagra. He was charged with seven counts of aggravated theft by deception. Lab tests last summer revealed the pills were made of water and wax.

10. *(The Express, April 24, 2000)* In the United Kingdom an inquiry has been launched by police into the availability of dangerous prescription drugs on the Internet. Detectives at the National Criminal Intelligence Service are carrying out the probe after doctors warned that lives were at risk.

11. *(Xinhua Nes Agency, April 17, 2000)* China will take effective measures to strengthen supervision over the quality

of medicine and stem fake products from flowing into the market, the State Drug Administration (SDA) announced here today. A sample survey of 8,501 kinds of medicine revealed that 754 failed to meet state standards. About 12 percent of the drugs available in drug stores or used in hospitals were of poor quality.

12. *(M2 Presswire, April 14, 2000)* The Medicines Control Agency (MCA) is conducting a national operation throughout England to combat the illegal sale of unlicensed skin lightening creams. There has been a considerable amount of counterfeit product. There has been particular concern that some products contain a high level of potent corticosteroids that can cause asthma and make the skin permanently thin.

13. *(The South African Crime Pages, April 10, 2000)* In South Africa the fake medicine scam in which a syndicate is selling stolen and counterfeit medicines as locally produced brand names is growing in leaps and bounds. Panic reportedly has set in at the top South African pharmaceutical companies whose brand names are being falsified and passed off as genuine products. This is suspected to be just the tip of the iceberg. The National Police Commissioner said their investigation had found the scam was being operated nationwide. The syndicate sells fake medicines from India, Pakistan and China as genuine South African products. All major pharmaceutical companies have launched their own investigations and may recall some of their products once the damage is known. Pharmaceutical companies are also concerned about the repackaging of expired medicines bearing their labels. Police have estimated pharmaceutical companies may have lost billions of rand through the scam in the last six years.

The syndicate was also linked to the hijacking of trucks distributing medicines in South Africa. The medicines were repackaged and re-routed to pharmacies. Machines used for weighing and counting pills and capsules were seized at the premises. Police also confiscated stickers, labels and pamphlets bearing South African pharmaceutical brand names.

14. *(Deutsche Presse-Agentur, March 29, 2000)* In Vietnam ten persons received sentences of up to 20 years in prison for producing and trading over 600,000 units of fake Viagra and other drugs. The counterfeits, which included fake ampicillin and the Aids treatment drug AZT, were made from a mixture of cassava starch and anti-mould powder and were sold in several southern provinces.

15. *New York Times, March 21, 2000)* Federal officials said that they had, for the first time, shut down foreign Web sites involved in the fast-growing business of selling prescription drugs over the Internet to American consumers. Agents of the United States Customs Service joined Thai authorities in raiding online pharmacies based in Thailand, which officials say is a major overseas source of powerful steroids, tranquilizers and other drugs that can be bought in the United States only with a prescription. Twenty-two people were arrested in Thailand and accused of violating Thai drug laws and export laws. Six people were arrested in Albany, New York, accused of buying drugs from a Thai online pharmacy. Federal officials said they were concerned about drugs imported from dozens of online pharmacies in Mexico, Switzerland, Britain, New Zealand and elsewhere. It is unclear whether those countries will cooperate with American investigators. In 1999, the Customs Service seized 9,725 packages with prescription drugs mailed to the

United States -- about 4.5 times as many as in the previous year. In the last six months, customs agents in New York, Los Angeles and Washington have seized more than 2,600 parcels of prescription drugs bought from Internet pharmacies in Thailand. Customs officials said the Thai pharmacies filled Internet orders with drugs obtained from what appeared to be a legitimate pharmacy in Bangkok. Employees took orders from the Web site, addressed envelopes, wrapped the drugs in newspaper and stuffed them inside greeting cards. Employees hid drugs in hollowed-out books, picture frames and jigsaw puzzle boxes, before shipping them to the United States, Germany, France and Japan. Parcels were sent by mail with no return addresses. The drugs were potentially dangerous because the controls over quality were lax. "A lot of this stuff is being cooked up in somebody's back room in Thailand," The drugs from overseas may be laced with all sorts of contaminants.

16. *(Scrip, February 25, 2000)* The Italian police are investigating the on-line sale of stolen pharmaceuticals. Since the end of last year, the Carabinieri antifraud squads (NAS) have been on the trail of Internet sites offering pharmaceutical products stolen from various locations around Italy. In one incident, an armed gang tied up staff in a warehouse near Rome and made off with some Lit5 billion ($2.5 million) worth of pharmaceuticals. Such robberies, as well as attacks on pharmacies and lorries carrying pharmaceuticals, are not uncommon in Italy, with the products generally being passed on to compliant pharmacists for resale. But now those involved are realizing the potential of the Internet as a medium for recycling stolen products. The NAS are also thought to be investigating suspicions that counterfeit and date-expired products are being offered for sale over the Internet.

17. *(Africa News, February 22, 2000)* Economic liberalization is to blame for the proliferation of unregistered drugs in the local market, a cabinet minister says. He said this has led to unscrupulous businessmen bringing in unregistered and counterfeit drugs into the local market.

18. *(Agence France Presse, February 15, 2000)* China's government, struggling to bring its wild-west pharmaceutical market under control, has banned Internet sales of medicine over safety concerns. The State Drug Administration (SDA) will temporarily prohibit sales of medication on-line. The administration acknowledged the country's pharmaceutical trade was "chaotic," with counterfeit and low-quality drugs common on the market, and warned e-commerce could allow illegal business to worsen.

19. *(Business World, February 4, 2000)* The Department of Health in the Philippines now has credibility problems when patients of public hospitals and clinics realized that the cheap or free antibiotics and cough preparations that came from government hospitals seldom worked or worked very poorly. Physicians and patients also know that the proliferation of fake, misbranded and adulterated medicines is of epidemic proportions more in the government hospitals than in the private ones.

20. *(AFX European Focus, February 1, 2000)* The number of fake medicine products on the Russian market increased by over 20 percent in 1999, the financial daily Vedomosti reported, citing official figures from the Russian ministry of health. The problem is not restricted to the most well known and effective products, it quoted Aleksandr Arzamastsev of the academy of medicine in Moscow as saying.

21. *(Agence France Presse, January 21, 2000)* Fake medicines are public health scourge in Congo. A burgeoning trade in contraband or outdated drugs is endangering public health in the equatorial African state of Congo, where authorities seem incapable of stamping out the traffic.

22. *(AFX News Limited, January 18, 2000)* The Chinese authorities have punished 132 companies for making and marketing bogus and substandard medicine, the China Daily reported. The businesses, which include manufacturers, sellers and hospitals, were found to be using fake medicines during a three-month investigation by the state drug administration, the China Daily said. The administration tested 8,350 batches of medicine from those companies and found nearly 7 percent were fake or substandard, SDA officials said.

23. *(The Independent, December 27, 1999)* In Bangladesh the local pharmaceutical companies are facing a serious challenge in as the market here is flooded with lower quality and cheaper smuggled Indian medicines and pesticides. According to sources, some of those drugs have been produced by fake medicine producers. Consumers are facing a serious threat due to the consumption of these medicines and pesticides. According to different sources, the smugglers can deliver inferior quality Indian medicines and pesticides within 24 hours of getting orders. The smugglers also found it easy to carry medicines in place of heavy goods from India. These low-quality medicines are not being prescribed by doctors in India itself. Sometimes the date expired smuggled medicines are updated with new expiry dates. Ranitidine, Femotidine, Canesten-V and other essential drugs are smuggled into the region.

24. *(Agence France Presse, December 21, 1999)* A growing racket in fake drugs must be halted with tougher legislation, India's health minister told parliament. Health and Family Welfare Minister N.T. Shanmugam told the upper house that operators making quick and illegal profits by duplicating leading pharmaceutical brands posed a huge health risk.

25. *(The Oil and Gas Journal, November 29, 1999)* Some of the pharmaceuticals that are available locally in states close to the Former Soviet Union are of dubious quality and origin. Many of the drugs are from the Former Soviet Union and often preparations that western physicians and patients are unfamiliar with. Also, there are counterfeit pharmaceuticals.

26. *(Agency WPS, October 22, 1999)* Russia is now under an avalanche of fake drugs. For the first 9 months of the year the Volgograd quality control and analysis laboratory declared 22 drugs brought to the region unfit for use. "This is too much", said the director of the regional Certification and Quality Control Center L. Kolesnikova. Besides, the flow of fake drugs into the region is increasing.

27. *(Federal News Service, October 21, 1999)* PREPARED TESTIMONY OF JAMES A. DAHL BEFORE THE HOUSE COMMITTEE ON THE JUDICIARY SUBCOMMITTEE ON COURTS AND INTELLECTUAL PROPERTY, SUBJECT - HEARING ON HR 2100, THE "ANTITAMPERING ACT OF 1999" In a FDA/OCI investigation counterfeit versions of a drug commonly prescribed to AIDS patients was found in commercial distribution channels. The code numbers and packaging were fraudulent and counterfeit, although the drug itself is believed to have been from a long outdated batch rejected years ago by the manufacture for quality reasons. In this case it is believed the criminals "invented" fraudulent code numbers for consumer packages. In other cases expensive prescription

[devices] used for the treatment of AIDS and other serious illnesses frequently surface in packaging bearing fraudulent code numbers. In many cases these drugs have been stolen from pharmacies, hospitals, commercials shippers, and warehouses. In some instances the drugs are believed to have originated in other countries where they are often produced in unknown, unregulated or possibly unsanitary environments. These criminals typically apply bogus code numbers to the packaging to extend the life of the drug and to cover up the true source of the product. [Additionally], an undercover FDA/OCI investigation in New York involved wholesale purchases of expensive fertility drugs. Fraudulent code numbers appeared on the counterfeit packaging containing these injectible products.

28. *(AP Worldstream, October 18, 1999)* Bogus malaria medication is being sold in Cambodia, threatening many of the 80,000 infected people here, health officials. "It is not poisonous," said Dr. Duong Vichet, director of the Cambodian Center for Combating Malaria, "but instead of getting cured, patients can quickly die because their health continues to worsen." Low-priced versions of anti-malarial medicines Mefloquine and Artesunate were recently found to be fakes packaged in bottles nearly indistinguishable from those used for the real medicine, he said.

29. *(Africa News, October 6, 1999)* Pharmaceuticals from India have earned a bad reputation in Tanzania where patients are giving them a wide berth reportedly because of their debased and at times suspect quality. A Dr. Ngiloi, surgeon at the Muhimbili Medical Centre in Dar es Salaam , testified that many patients reject India-manufactured drugs because of their bad reputation and because they were too cheap to be trusted to cure disease. "There have been cases where drugs ordered from India arrive with black spots, or bad smell: In case of capsules, they may arrive melted or virtually empty,"

Dipen Shah of the Tanzania Pharmaceutical Manufacturers Association said. He claimed that there have been cases where capsule drugs were stuffed with cassava flour instead of the necessary pharmaceuticals. India boasts of up to 20,000 pharmaceutical manufacturing industries and Tanzanians say the number is too big for the government of India to control them effectively.

30. *(Africa News, September 28, 1999)* All registered pharmacies will display a new emblem as a first step in curbing the proliferation of unregistered drug shops in Kenya. The head of the Green Cross project says they have been forced to introduce the new sign emblem by the proliferation of unregistered pharmacies selling counterfeit or stolen medicines.

31. *(Birmingham Post, September 23, 1999)* In the United Kingdom arrests have been made after police smashed what they believe to be a multi-million pound smuggling ring to import fake Viagra from India. Detectives believe the tablets were to be sold as Viagra and the packaging would also be mimicked to create the illusion that the tablets were genuine.

32. *(Bangkok Post, September 13, 1999)* Concern has been raised over the increased smuggling of fake medicines in provinces on both sides of the Thai-Cambodian border. The issue was discussed at yesterday's joint meeting of Thai and Cambodian health authorities at the national, provincial and local levels. The counterfeit drugs did not contain active ingredients as specified on their labels. Food and Drugs Administration secretary-general Mongkhol na Songkhla said Thailand has sought assistance from the World Health Organisation in combating counterfeit drugs, most of which are observed to be coming from countries outside the Asean region. The use of substandard drugs has been one of the main causes of drug-resistant malaria along border areas.

33. *(Africa News, September 3, 1999)* In South Africa pharmaceutical companies are now using their own security guards to prevent theft. Two Cape Town pharmaceutical wholesalers have been raided and stock believed to have been stolen seized in the latest round of an on-going battle against rampant medicine crime that is estimated to cost the industry close on R2-billion a year. Medicine destined for state hospitals will now also be packaged exclusively, different from that intended for the retail market, in an effort to address overwhelming theft from hospitals and clinics. One company said the company was employing its own investigators in an effort to safeguard business. Special foil, although more expensive, that was more difficult to copy is now being used as packaging. Hospitals and airports were two areas where drugs were illegally re- routed. Generic and parallel imports were routinely repackaged and stocked past its sell-by date. Manufacturer excess and bulk loose tablets or capsules were also stolen and packed for sale. International estimates are that as much as 7% of all medicines on pharmacy shelves worldwide are counterfeit. About 60% of all pharmaceuticals on the Nigerian market are believed to be counterfeit - some made locally and some imported.

34. *(Xinhua News Agency, August 29, 1999)* Tanzania is getting tough on fake or substandard pharmaceuticals, mostly from India, in an effort to safeguard people's health. The ministry of health was registering all pharmaceuticals and started to send full-time drug inspectors to all major ports in a bid to curb the entry of fake or substandard ones. The move comes after a number of medical practitioners and the public complained that some imported drugs were ineffective. Most complaints were directed at drugs made in India. The influx of fake pharmaceuticals has been an issue of concern of the Pharmacy Board. The Indian high commissioner to Tanzania,

said earlier this week that drugs from India were used worldwide and consumers need not worry about the manufacturing processes. He said the United States purchases about 35 percent of Indian made pharmaceutical products while European countries buy another 25 percent to 35 percent.

35. *(Africa News, August 9, 1999)* In Nigeria multinational drug manufacturers find it difficult to tell their drugs from the fake. Counterfeiters compromise standards by reducing the active ingredients in the medicine. Counterfeiters go to the Far-East countries like Taiwan and approach a manufacturer with the genoprototype of a particular drug produced in Nigeria and say, 'look, produce this drug for me but reduce the active ingredients by 30 per cent. Let the batch number, pack and everything be the same.' These are then mixed with the original in circulation. This is how big-time faking goes on in Nigeria.

36. *(Africa News, July 21, 1999)* The Malawi Pharmacy, Medicines and Poisons Board has issued a warning that the country has been flooded with fake drugs which pose a threat to life. The fake medicines include pain-killers like Cafemol with labels of Pharmanova Zambia, Norol and Panadol and Tanzania Asprin from Mansoor Daya Chemicals and Shelys Pharmaceuticals and Parapain capsules from as far as India.

37. *(Chemical Business Newsbase, July 20, 1999)* Fake medicines and drugs including Ecstasy pills and raw materials, have been seized in raids in Malaysia. Also seized during the raid were illegal cough mixtures, fake eye drops and imitation paracetamol tablets. The raid recovered grinding machines, moulds, ovens and raw materials used to

produce the pills and medicine. About 5kg of raw materials were found at the scene, enough to make one million pills.

38. *(Agence France Presse, July 16, 1999)* Indian drug manufacturers have launched a campaign against fly-by-night operators making quick and illegal profits by duplicating leading pharmaceutical brands. In India these fake medicines are made without any drug content -- by merely copying the size, color and shape of the dosage and package.

39. *(Marketletter, June 14, 1999)* A recent inspection of state-owned and private pharmacies, hospitals and outpatient clinics in the Tajikistan capital of Dushanbe has found that a number of illegal factories producing fake medicines, which are then sold in large quantities by local pharmacies. There are now numerous criminal cases against heads of pharmacies responsible for selling fake medicines, but many of them have not been carried through to their conclusion. Some pharmacies which were closed by the law enforcement agencies are still continuing to operate.

40. *(Africa News, April 30, 1999)* The National Medical Stores (NMS) at Entebbe has banned import of catheters from India, saying they are substandard. Counterfeit drugs are on the increase, largely from India," a Mulago hospital doctor said.

41. *(Marketletter, March 15, 1999)* Lower prices and fewer regulations, resulting in easy patient access to prescription drugs in Mexico, are drawing US consumers away from American pharmacies, according to a study by Marvin Shepherd, director of the Center for Pharmacoeconomics at the University of Texas' College of Pharmacy in Austin. Several other studies have reported 25% of US residents who enter Mexico as tourists buy pharmaceuticals, and that 61%

traveling to Mexico to purchase medicines do so primarily because of price differences. It is not uncommon for commercial pharmacies in Mexico to dispense them without a prescription. In some cases, the report also noted, drugs produced in Mexico have been found to be counterfeit.

42. *(FT Asia Intelligence Wire, November 27, 1998)* Self-medication is a way of life for Malaysians but the question that remains to be answered is, how safe and effective is this over the counter treatment. Dr.S.T. Han, regional director of World Health Organisation (WHO) for Western Pacific Region, said counterfeit drugs ranging from well-known brands to sub-standard drugs with or without active ingredients, were an increasing problem. "It represents a particular problem for self-medication because public finds it more difficult than prescribers, pharmacists and other drug sellers to identify such drugs," he said.

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Africa News

May 18, 2000

SECTION: NEWS, DOCUMENTS & COMMENTARY

LENGTH: 546 words

HEADLINE: Benin;
Benin Expresses Concern Over Counterfeit Drugs

BYLINE: Panafrican News Agency

BODY:

Dakar, Senegal (PANA) - A senior official from Benin's health ministry, has expressed concern at the growing utilisation of counterfeit drugs, particularly among poor countries.

Dr Idrissou Abdoulaye told the ongoing session of the World Health Assembly in Geneva that poor people buy these dangerous drugs because they are cheap.

"Every day people die because of counterfeit drugs," Abdoulaye was quoted by a World Health Organisation news release as telling the five-day assembly, which ends Friday.

He did not give an exact death toll but said the number of people using such drugs was high: "How many? We'll never know. But they keep buying these drugs because they're cheaper," he added.

Dr Yasuhiro Suzuki, WHO executive director in charge of Health Technology and Pharmaceuticals, said "fighting this global problem puts an additional burden on health systems that are often already over-stretched."

He added "no country is immune from the threat of counterfeit drugs but those with weakly regulated pharmaceutical markets suffer most."

The discussion on the multi-faceted problem attracted many senior health officials, representatives of non-governmental organisations, pharmaceutical industry, as well as Interpol.

The criminals are running highly sophisticated operations taking advantage of cross-border loopholes.

Supplies, production, shipping, re-labelling, financing, distribution are all handled in different countries.

"The most common way of describing counterfeit drugs in customs forms is to declare "harmless pharmaceutical substances of no commercial value," Guy Woods of the Lacuna Research Ltd explained.

The Philippines has made a start in dealing with the problem by adopting a special law on counterfeit drugs in 1996, which facilitates random sampling and monitoring of drug quality in pharmacies and hospitals.

It also imposes heavy penalties for offenders: from six months to life imprisonment along with a hefty 25,000 US dollars fine.

Nazarita Lanuza, head of the country's Food and Drug Bureau, said, however, that the problem can only be curbed if many countries co-operate.

"We need co-operation with WHO. This fight is a co-operative undertaking. We cannot do it alone," she said.

One of the identified hitches was the lack of common definition of what constitutes counterfeit drugs.

In some countries production of counterfeit drugs is described as fraud while in others the term is "production of counterfeit substances."

As a result, even Interpol would not have a unified database. There is an urgent need for closer co-operation between law-enforcing agencies, legislative bodies and pharmaceutical industry.

"A deadly combination of demand for cheap drugs and fat profit margins makes counterfeit drugs irresistibly attractive to greedy criminals," Suzuki commented. "Clearly, there is an urgent need for action if unnecessary human suffering is to be stopped."

To further support efforts by countries to combat this problem, a working group has been established with WHO, International Federation of Pharmaceutical Manufacturers Associations, International Generic Pharmaceuticals Alliance, World Self-Medication Industry and Pharmaciens sans Frontieres (Pharmacists Without Borders).

LANGUAGE: ENGLISH

LOAD-DATE: May 18, 2000

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February 1, 2000

SECTION: Business

LENGTH: 400 words

HEADLINE: New DoH rules pave way for parallel drug imports

BODY:

The Department of Health (DoH) has amended the implementing rules and regulations (IRR) of Republic Act 8203 or Counterfeit Drug Law, lifting legal restrictions on parallel importation of drugs and other pharmaceutical products.

The DoH amended Rule 1 Section H of the IRR which classified parallel imported drugs as "counterfeit." The DoH deleted the IRR provision which states that: "If the unregistered imported drug product has a registered counterpart brand in the Philippines, their product shall be considered counterfeit."

Health Secretary Alberto G. Romualdez, Jr. said the amendment would now allow parallel importation of drugs. Parallel importation of drugs has long been eyed by the Health department as a measure to lower drug prices in the country.

Two public hearings were held last January 17 and 20 regarding the proposed amendment to the IRR.

"This provision essentially is an obstacle to parallel import. So by amending this, it makes possible parallel imports, without violating the law on counterfeit drugs," Mr. Romualdez told newsmen during a briefing at the DoH compound in Sta. Cruz, Manila.

Despite the new rules, Mr. Romualdez said not everybody can engage in parallel importation. The issue on who will be allowed to engage in parallel importation of drugs, he said, still needs further discussions with the Department of Trade and Industry and drug suppliers.

Mr. Romualdez also admitted that both foreign and local pharmaceutical companies have raised opposition against parallel importation of drugs. He said these companies claimed that parallel importation would violate the Intellectual Property Code; the Food, Drug and Cosmetics Act; and even the Generics Law.

However, Mr. Romualdez said the issue the amendment addresses is "not parallel importation per se but rather the principle that counterfeit drugs must be something that is talagang bulok (really lacking in quality)."

"Basta pareho ang brand (provided that the brands are the same) and the brand comes from a supplier that is accredited by the owner of the brand, then it should not be classified as counterfeit," Mr. Romualdez said.

Should sanctions be imposed on sale of these drugs, the sanctions should not be those provided for in the penal provisions of the counterfeit drug law, he said.

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LANGUAGE: English

LOAD-DATE: February 1, 2000

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May 19, 2000, Friday

SECTION: International news

LENGTH: 527 words

HEADLINE: More sub-standard medicines spread in worldwide traffic

BYLINE: Catherine Rama

DATELINE: GENEVA, May 19

BODY:

More poor quality or counterfeit medicines are being traded across the world, participants at a World Health Organisation (WHO) conference were told this week.

According to the latest figures, 771 cases of counterfeit medicines were reported to the WHO up until April 1999. Of 325 of the cases which have been reported on, 59 percent contained no active molecules, 17 percent were incorrectly mixed, 16 percent contained other products and only seven percent contained the correct mixture of the appropriate drug.

The WHO began a campaign two years ago to help member states to fight counterfeit medicines in partnership with the pharmaceutical industry, saying that use of the counterfeits could be fatal.

It cited the 1995 case of some 2,500 people who died in the west African state of Niger after being inoculated with a fake vaccine against meningitis.

In the same year 89 people died in Haiti after swallowing doses of a cough mixture made of paracetamol and glycol, a toxic chemical used as an anti-freeze in automobile cooling systems.

But a WHO document said that information on the problem was insufficient, adding that no worldwide study was being carried out on the problem.

"We lack information for our data bank," said Michael Holstein, a counterfeit drug specialist with Interpol. He called for a "structured regional approach" involving governments, industrialists and non-governmental organisations, plus an information campaign to the public.

Doctor Margarit Den Boer, a member of the Netherlands section of Medecins Sans Frontieres (MSF - Doctors Without Borders), criticised those multinationals which marketed drugs under the same name but of differing qualities, depending on their destination -- developing countries or the developed world.

Doctor Jean-Yves Videau, of the Medico-Pharmaceutical Humanitarian Centre based in Clermont-Ferrand, central France, carries out between 350 and 400 analyses a year.

He said he had been surprised to find that basic inputs were of increasingly uncertain origin and that quality was declining. "The purer it is, the dearer it is," he said.

He insisted that the dosage of ingredients should be scrupulously respected, especially in the case of antibiotics where under-dosing could build up resistance among patients.

Den Boer blamed the increased trading in counterfeit drugs on ineffective legisation in developing countries.

MSF believes that the fight against fake drugs should be encouraged by the manufacture of generic medicines in the developing countries, with introduction of strict regulation of drugs, with technical assistance from the WHO.

Nazarita Lanuza, of the Philippines, cited the case of her own country which adopted strengthened legislation in 1966.

Offenders can now be sentenced to jail terms ranging from six months to life while maximum fines were hiked from 125 dollars (140 euros) before 1996 to 25,000 dollars.

"In spite of this, fake drugs are continuing to proliferate," she said. "We need full support from governments, the police, customs services and the industrial sector to take effective joint action," she said.

cr/agv/sw

LANGUAGE: ENGLISH

LOAD-DATE: May 19, 2000

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South China Morning Post

July 6, 1999

SECTION: Pg. 6

LENGTH: 280 words

HEADLINE: Counterfeit stroke medication sold over border in locally-made packaging

BYLINE: ALISON SMITH

BODY:

Stroke victims are being sold totally ineffective counterfeit medication on the mainland through a syndicate using Hong Kong packaging.

The genuine manufacturer of the intravenous drug Cerebrolysin, Health Care Pharmaceuticals (China) Ltd, instigated a private investigation that led to the conviction of Lai Shu-lam, whose Forest Offset Printing Co provided thousands of printed packages and instruction leaflets for the fake drug.

Lai was ordered yesterday to pay a $30,000 fine or face two weeks' jail for contempt of court by Mr Justice Wally Yeung Chun-kuen at the Court of First Instance.

The judge agreed Lai had failed to hand over stocks of the packages and documents which the manufacturers hoped would lead them to a mastermind in the syndicate.

Acting on a tip-off, Health Care Pharmaceuticals (China) Ltd obtained a court order against Lai in September ordering him to reveal the names of others involved and to hand over any counterfeit goods or documents relating to the drug's production.

Lai said a "walk-in" customer called Mr Cheng had paid a deposit for about 200,000 packages and he had no idea how to contact him.

Investigations revealed Lai had hundreds of counterfeit instruction leaflets in a desk drawer, that he understated the order and that he had fulfilled another order - altogether totalling 340,000 boxes - which he did not disclose to the court.

The judge ordered Lai to pay costs of the action along with the $30,000 fine.

Health Care Pharmaceuticals (China) Ltd managing director George Cautherley said: "We've seized three different counterfeit formulations - none of which contained the proper product."

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THE JOURNAL (Newcastle, UK)

July 16, 1999, Friday Edition 1

SECTION: REGIONAL NEWS,

Pg. 3

LENGTH: 421 words

HEADLINE: Raids seize fake drugs - Tyneside haul worth millions

BYLINE: by Angela Upex Crime Reporter

BODY:

COUNTERFEIT drugs with a street value of millions of pounds have been seized.

Officials from the Medicine Control Agency assisted by Northumbria Police carried out an operation in Tyneside and other parts of the North-East. Detectives from the Crime Team South and the agency, which investigates unlawful activity involving medicines, have been investigating the supply of counterfeit drugs to body builders across the region.

Officers executed search warrants at commercial addresses and homes in Byker, Team Valley, Heworth, East Boldon and Newcastle City centre.

They seized huge quantities of injection phials, boxes and labels purporting to be a prescription-only drug. It is believed the drug is Nebain, which is a steroid-rich drug used in general medicine, known to be abused by bodybuilders to build up muscle.

The haul is the biggest seized by the Medicine Control Agency, according to police.

The agency's primary function is to safeguard public health by ensuring that all medicines on the UK market meet appropriate standards of safety and quality.

Officers said last night that one entire office had been filled from floor to ceiling with boxes of the drugs and medicines which are believed to have been illegally manufactured in the region.

During the operation two men were arrested for allegedly conspiring to produce a controlled drug.

They have both been released on bail pending further inquiries and analysis of the seized materials.

Last month detectives arrested five people after finding thousands of steroids and prescription drugs at a house in North Shields. They are suspected to have been illegally imported for selling across the region.

Police found 18,000 diazepam tablets and 5,000 steroids.

They also discovered 58,000 ephedrine tablets, a performance enhancing drug banned by sports organisations.

A Department of Health spokeswoman said she could not comment on details of the latest case because the investigation was still continuing.

She said: "We can confirm that there has been a joint Northumbria Police and Medicine Control Agency investigation involving the production of unlicensed medicinal products."

Bodybuilders who routinely misuse bodybuilding steroids risk serious effects on their health.

Many body-builders believe these substances will help them to be faster or stronger and help to achieve maximum performance.

However, they can cause health problems which include malfunctioning of the liver, kidneys and heart.

LOAD-DATE: July 17, 1999

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Marketletter

May 22, 2000

SECTION: Pg. NA ; 0951-3175

IAC-ACC-NO: 62170004

LENGTH: 292 words

HEADLINE: US FDA slammed over counterfeit bulk drugs.

AUTHOR-ABSTRACT: THIS IS THE FULL TEXT: COPYRIGHT 2000 Marketletter Publications Ltd. Subscription: 499.00 British pounds per year. Published weekly. 54-55 Wilton Road, London SW1V 1DE., United Kingdom

BODY:

A lack of leadership at the US Food and Drug Administration and weakness in its import system has left the USA vulnerable to potentially counterfeit, substandard, contaminated or poisoned imports of bulk drugs, House Commerce Committee chairman Tom Bliley has told FDA Commissioner Jane Henney.

In a letter detailing nearly two years of investigations by the Committee, Rep Bliley says that the FDA "has little or no control of imported counterfeit bulks entering the USA, providing no meaningful deterrence to trafficking of these products."

The letter details the case of imported gentamicin sulfate, particularly that supplied by Long March Pharmaceutical of China. From 1989 to August 16, 1994, the product was associated with 1,974 adverse events including 96 disabilities and 49 deaths. The FDA issued an import alert on Long March's product in September 1999, but FDA data show 254 adverse events associated with it from May 1, 1999, to January 11, 2000, including 202 serious events and 17 deaths.

"I am concerned that Long March bulk drugs and/or counterfeit gentamicin sulfate from China may still be entering the US health care system," he says.

Following the letter's publication, FDA Center for Drug Evaluation and Research director Janet Woodcock told Reuters Health that the agency had the gentamicin issue under control. Imports of all drugs from Long March have been halted, and there have been no further adverse events associated with its gentamicin, she said. While agreeing that the agency should do more in this area, she noted its limited resources and problems associated with inspecting foreign firms. The globalization of the pharmaceutical industry had posed a real challenge in this area, she added.

LANGUAGE: ENGLISH

IAC-CREATE-DATE: May 18, 2000

LOAD-DATE: May 19, 2000

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Chemical News & Intelligence

May 18, 2000

LENGTH: 218 words

HEADLINE: Mexico's pharma industry seeks crackdown on bogus drugs

SOURCE: Chemical News & Intelligence

BYLINE: Joe Kamalick

DATELINE: Houston/ MEXICO

BODY:

Pharmaceutical industry officials said Thursday they are seeking federal government action against a Mexican company they accuse of manufacturing counterfeit drugs and supplements.

Rafael Gual Cosio, executive director of the Association for Pharmaceutical Industry Investigations (AMIIF), told CNI Thursday his group has filed a formal complaint with the federal Health Secretary alleging counterfeit drugs manufacturing and tax evasion by the single firm.

Gual said: "We have tested a number of these supposedly generic products currently on sale at pharmacies throughout the country and have found that are not what they claim to be and can cause damage to one's health."

AMIIF said the drugs, including those sold under the names Acylovin, Naproxen and Flunarizina, are being sold in more than 200 retail outlets throughout Mexico at prices up to 75% cheaper than the brand-name products they duplicate. AMIIF warned that, according to its own independent testing, the substitute drugs are not chemically equal to the originals.

Gual said AMIIF also has called on the consumer affairs group, Profeco, to investigate these products.

Gual said: "This is not just about commercial loss within the industry. This is about the destruction of product image and a public health risk."

LANGUAGE: English

LOAD-DATE: May 24, 2000

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Chemical News & Intelligence

July 20, 1999

LENGTH: 190 words

HEADLINE: DuPont Pharma sues Mexican firm on drug

SOURCE: Chemical News & Intelligence

BYLINE: Mary Ann Tawasha

DATELINE: HOUSTON

BODY:

DuPont Pharmaceuticals has filed a patent infringement lawsuit with the Mexican Institute of Industrial Property against Syncor de Mexico, a subsidiary of Syncor International, DuPont announced Tuesday.

No one from Woodland Hills, California-based Syncor was immediately available for comment.

DuPont filed its suit on 17 June after gathering evidence during several months of investigation and product testing, according to DuPont. The suit charges that Syncor has engaged in the illegal purchase and sale of DuPont's heart imaging agent, Cardiolite, in Mexico, including the purchase and sale of counterfeit Cardiolite not manufactured by DuPont.

The Mexican government is conducting an ongoing investigation into the matter, according to DuPont.

"We are extremely disappointed that Syncor apparently has betrayed our trust by trading in counterfeit Cardiolite in Mexico," said William DeLorbe, executive vice president of DuPont Pharmaceuticals' medical imaging division in North Billerica, Massachusetts.

DuPont said Syncor has been its preferred distributor of Cardiolite in designated areas of the US since 1994.

LANGUAGE: English

LOAD-DATE: July 26, 1999

Mr. UPTON. Copies are provided to the witness as well.

Some of the FDA internal documents reveal that over the last few years key FDA officials believe counterfeit imported bulk drugs to be associated with deaths and other serious adverse events in American patients. This is the first time many of these documents have come to light.

The international community is also increasingly concerned. Just last month, the World Health Organization and international pharmacists and international drug manufacturers publicized their concerns about counterfeit drugs. Some have estimated that 50 to 70 percent of the drugs in some developing countries are counterfeit.

It would be wrong to assume that the U.S. is immune to the documented counterfeiting in international pharmaceutical trade. The World Health Organization and some industry analysts estimate that about 5 to 8 percent of drug products shipped to the U.S. are counterfeit, unapproved or substandard.

Counterfeit bulk drugs are ingredients in human prescription drugs which are deliberately and fraudulently mislabeled or misbranded with respect to its identity or source. Without knowledge of the source, there is no product history. Without product history, the safety and efficacy of the product cannot be assured because there is no information about impurities, the age, the storage, the manufacturing environment or even the synthesis of the product.

It is extremely difficult to detect counterfeit bulk drugs because there is no single chemical test for all impurities that may be in the product.

Counterfeit bulk drugs can represent a serious threat to the public health. A bulk quantity of as little as 50 kilograms can be used in the production of millions of tablets or capsules. Therefore, only one counterfeit bulk that contains an impurity or is synthesized improperly could cause immediate death or injury to numerous people.

The result of a counterfeit could be that the medication will not be as effective or could produce a long-term disease or injury. For example, these pictures being shown over here to the right show the differences at a microscopic level between the authentic drug and the counterfeit drug. The difference in this case lies in the particle size. Such a difference in the particle size could mean that the drug doesn't get absorbed into the blood stream and therefore doesn't work.

There is still much we do not know about the public health threat. The FDA has not made any public health assessment of the issue. Even if the FDA attempted such an assessment, the FDA has no ability to make an assessment with its current data.

In its March 5, 1999, letter to Congressman Klink and myself, the FDA stated that it does not collect data to assess the amount of unacceptable or adulterated active pharmaceutical ingredients shipped to the United States from foreign sources.

With what information the FDA does have, the FDA has linked counterfeit or unapproved bulk drugs to deaths and other adverse events in the United States. Last year, when FDA's Forensic Chemistry Center conducted a focused, in-depth study of just a handful of Chinese drug imports, evidence was uncovered which led in part to targeted inspections, resulting in an import alert for one plant and warning letters for two other plants. We know we are seeing only the tip of the iceberg.

Lured by high prices and potential profits in the United States, counterfeit bulks can get into our prescription drugs in several ways: one, as imported ingredients to the U.S. manufacturers; two, as imported ingredients to pharmaceutical compounders; and three, as source ingredients for Internet pharmacies marketing to the United States.

The counterfeiters use sophisticated methods, such as preparing false labeling, containers, seals and certificates of analysis, or using a manufacturing process that differs from the filed manufacturing process.

Here are two examples; the first example involves three pictures. The first picture shows a document dated around 1989 from an industry consultant, laying out a scheme to market unapproved Chinese trimethoprim under the approved label of a German company.

The second picture shows that the signature from the first document belongs to Dr. Jose Gomes.

The third picture shows that Dr. Gomes, in 1999, was the consultant for Long March Pharmaceutical, the firm that made gentamicin sulfate that I talked about a little bit earlier.

The second example is a diagram of how a drum of bulk drugs shipped to Australia was counterfeited. A layer of authentic drug on the top, milled sugar in the next layer, followed by a layer of authentic drug, et cetera.

The public policy implications are enormous. Public health is threatened by unapproved, substandard or counterfeit bulk drugs. Counterfeits could have direct impact on the integrity of the adverse drug event report system. Counterfeit bulk drugs not only hurt patients but defraud Medicare and Medicaid programs that pay for these drugs as if they are authentic.

There is also speculation that an unknown influx of counterfeit unapproved drugs is leading to more drug and chemical allergies and more antibiotic resistance.

Even after years of plans and recommendations from internal working groups, the FDA remains largely unable to detect or control imported counterfeit bulk drugs from entering the U.S. The FDA has not worked with the Customs Service to investigate imported counterfeit bulk drugs since 1996 and, as far as I know, does not have any ongoing criminal enforcement action or even a known strategy to deter or prevent crimes connected to counterfeiting bulk drug imports. Instead, the FDA relies on a regulatory system of inspections, import policies and post-marketing surveillance.

However, the FDA's testimony on this system is not great. To illustrate this point, here are some direct quotes from the documents.

"The agency is hindered by not having a complete list of foreign facilities manufacturing drugs products for the United States."

That's not acceptable. Those are my words.

"We still don't have systems that can effectively and efficiently communicate across the agency or readily provide field staff with critical information."

Again, that's not acceptable.

"The drug listing data base also does not interface with OASIS, which would assist import officers by automatically comparing manufacturers and listed pharmaceutical products to products offered for importation."

Again, that's not acceptable.

"FDA has identified the need to establish enhanced procedures to better assure that an import alert notice for a product or company will, in fact, prevent the violative products from reaching the U.S. consumer."

Again, the same response.

"The drug listing does not ensure authentic sources or authentic material, as described in new drug applications, is in fact being offered for admission."

In addition, the FDA told us that they only have information on 18 percent of the foreign drug manufacturers that ship to the United States. Only 18 percent. The FDA has no information on 623 importing drug firms from China and 409 importing drug firms from India. No information.

These kinds of weaknesses and others cause me to conclude that the FDA cannot assure the American people that prescription drugs are free from counterfeits and poorly made, unknown ingredients. The FDA has told this committee that its safety net is being stretched by the increasing global nature by the pharmaceutical commerce. At some point, FDA's safety net will in fact break, and I fear that it already may be broken.

It is urgent that the FDA shift to a new model to deal with counterfeit bulk drug imports. I am ready to do more than just hold FDA accountable; I am committed to working for a solution to this serious and dangerous problem. I intend to fully work with Commissioner Henney and the FDA to develop and implement new, effective protections, but the FDA needs to be forthright today about the threat and what it will really take to deal with the problem.

I look forward to the testimony and further discussion and action by the Congress, Republicans and Democrats, and the administration.

At this point, I yield to my friend and colleague from the great State of Michigan, Mr. Stupak.

[The prepared statement of Hon. Fred Upton follows:]

PREPARED STATEMENT OF HON. FRED UPTON, CHAIRMAN, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

Today we're here to dissect the issue of the influx of counterfeit bulk drugs. There is increasing concern that drug ingredients made overseas that are either counterfeit, unapproved, or poorly made are entering our nation's health care system and endangering patients' health and even lives.

Here's the case in point. Several years ago, 89 Haitian children died after taking cough medicine made with contaminated glycerin traced to China. We may think that tragic events like this can't happen here in our country, with its sophisticated regulatory system. But our Committee's investigation reveals that our system has major flaws—and, it could happen here—all too easily.

Recently, our Committee's investigation revealed that FDA had linked the adverse reactions of 155 American patients to gentamycin sulfate made by Long March Pharmaceutical, a Chinese drug company. It may well be that other patients died from unknown impurities in this drug. FDA's own forensic tests showed unexplained discrepancies between the chemical fingerprints of the drug taken from Long March at different times. FDA's inspection revealed data integrity problems and other serious deficiencies with Long March. Despite FDA inspections and quality control by the U.S. drug companies that used this material, this suspicious bulk drug still infiltrated our healthcare system without detection. This is just one example of other instances that have confirmed that counterfeit, substandard drug imports are getting into our prescription drug supply and harming patients.

To substantiate our concerns about counterfeit bulk drugs infiltrating our nation's health care system, I now ask unanimous consent to place FDA correspondence, internal FDA documents, and articles on drug counterfeiting into the record documenting the counterfeit bulk drug problem. Some of the FDA internal documents reveal that over the last few years key FDA officials believe counterfeit imported bulk drugs to be associated with deaths and other serious adverse events in American patients. This is the first time many of these documents have come to light.

The international community is also increasingly concerned. Just last month, the World Health Organization, international pharmacists, and international drug manufacturers publicized their concerns about counterfeit drugs. Some have estimated that 50-70% of the drugs in some developing countries are counterfeit. It would be wrong to assume that the United States is immune to the documented counterfeiting in the international pharmaceutical trade. The World Health Organization and some industry analysts estimate about 5-8% of drug products shipped to the U.S. are counterfeit, unapproved or substandard.

Counterfeit bulk drugs are ingredients in human prescription drugs which are deliberately and fraudulently mislabeled or misbranded with respect to its identity or source. Without knowledge of the source, there is no product history. Without product history, the safety and efficacy of the product cannot be assured because there is no information about impurities, the age, the storage, the manufacturing environment, or the synthesis of the product. It is extremely difficult to detect counterfeit bulk drugs because there is no single chemical test for all impurities that may be in the product.

Counterfeit bulk drugs can represent a serious threat to the public health. A bulk quantity as little as 50 kilograms can be used in the production of millions of tablets or capsules. Therefore, only one counterfeit bulk that contains an impurity or is synthesized improperly could cause immediate death or injury to numerous people. The result of a counterfeit could be that the medication will not be effective or could produce a long term disease or injury. For example, these pictures show the differences at a microscopic level between the authentic drug and the counterfeit drug. The difference in this case lies in the particle size. Such a difference in the particle size could mean that the drug does not get absorbed in the bloodstream and therefore doesn't work.

There is still much we do not know about this public health threat. The FDA has not made any public health assessment of this issue. Even if FDA attempted such an assessment, the FDA has no ability to make an assessment with its current data. In its March 5, 1999, letter from Congressman Klink and me, the FDA stated that it does not collect data to assess the amount of unacceptable or adulterated active pharmaceutical ingredients shipped to the U.S. from foreign sources. With what information the FDA does have, the FDA has linked counterfeit or unapproved bulk drugs to deaths and other adverse events in the U.S. Last year when FDA's Forensic Chemistry Center conducted a focused, in-depth study of just a handful of Chinese drug imports, evidence was uncovered which led in part to targeted inspections resulting in an import alert for one plant and warning letters for two other plants.

We know we are only seeing the tip of the iceberg.

Lured by high prices and potential profits in the U.S., counterfeit bulks can get into our prescription drugs in several ways: (1) as imported ingredients to U.S. manufacturers; (2) as imported ingredients to pharmaceutical compounders; and (3) as source ingredients for interact pharmacies marketing to the U.S. The counterfeiters use sophisticated methods such as preparing false labeling, containers, seals and certificates of analysis, or using a manufacturing process that differs from the filed manufacturing process.

Here are two examples. The first example involves three pictures. The first picture shows a document dated around 1989 from an industry consultant laying out a scheme to market unapproved Chinese trimethoprim under the approved label of a German company. The second picture shows that the signature from the first document appears to belong to Dr. Jose Gomes. The third picture shows that Dr. Gomes in 1999 was the consultant for Long March Pharmaceutical, the firm that made the gentamicin sulfate I talked about earlier. The second example is a diagram of how a drum of bulk drug shipped to Australia was counterfeited. A layer of authentic drug on the top, milled sugar in the next layer, followed by a layer of authentic drug, etc.

The public policy implications are enormous. The public health is threatened by unapproved, substandard or counterfeit bulk drugs. Counterfeits could have direct impact on the integrity of the adverse drug event report system. Counterfeit bulk drugs not only hurt patients, but defraud Medicare and Medicaid programs that pay for these drugs as if they are authentic. There is also speculation that an unknown influx of counterfeit, unapproved drugs is leading to more drug and chemical allergies and more antibiotic resistance.

Even after years of plans and recommendations from internal working groups, the FDA remains largely unable to detect or control imported counterfeit bulk drugs from entering the U.S. The FDA has not even worked with the Customs Service to investigate imported counterfeit bulk drugs since 1996 and does not have any ongoing criminal enforcement action—or even a known strategy—to deter or prevent crimes connected to counterfeiting bulk drug imports. Instead, FDA relies on its regulatory system of inspections, import policies, and postmarketing surveillance. However, the FDA's testimony on this system is devastating. To illustrate this point, here are some direct quotes from FDA documents.

"The Agency is hindered by not having a complete list of foreign facilities manufacturing drugs products for the U.S."

This is not acceptable,

"[W]e still do not have systems that can effectively and efficiently communicate across the Agency, or readily provide field staff with critical information they need."

This is not acceptable.

"The Drug Listing database also does not interface with OASIS, which would assist import officers by automatically comparing manufacturers and listed pharmaceutical products to products offered for importation . . ."

This is not acceptable.

"FDA has identified the need to establish enhanced procedures to better assure that an import alert notice for a product or company, will, in fact, prevent the violative products from reaching the U.S. consumer."

This is not acceptable.

"The drug listing does not ensure authentic sources or authentic material as described in New Drug Applications (NDAs) is in fact being offered for admission."

This is not acceptable,

In addition, the FDA told us they only have information on 18% of the foreign drug manufacturers that ship to the U.S. The FDA has no information on 623 importing drug firms from China and 409 importing drug firms from India. These kinds of weaknesses, and others, cause me to conclude that the FDA cannot assure the American people that prescription drugs are free from counterfeits and poorly made, unknown ingredients. The FDA has told the Committee that its safety net is being stretched by the increasingly global nature of pharmaceutical commerce. At some point the FDA's safety net will break, and I fear it may already be broken. It is urgent that the FDA shift to a new model to deal with counterfeit bulk drug imports.

I am ready to do more than just hold FDA accountable. I am committed to working for a solution to this serious and dangerous problem. I fully intend to work with Commissioner Henney and the FDA to develop and implement new, effective protections. But the FDA needs to be forthright today about the threat and what it will really take to deal with the problem. I look forward to the testimony, further discussion, and action.

Mr. STUPAK. Thank you, Mr. Chairman. I want to thank you for holding this hearing, and I will be brief.

You certainly in your outline—in your testimony, it was outlined that we cannot tolerate the sale of illegal and potentially adulterated pharmaceuticals in the market. Obviously, patient safety is compromised when drugs are imported that are manufactured without quality controls and inspections.

I am interested to hear, Mr. Baker, about the Food and Drug Administration's attempts to prevent and punish illegal bulk drug sales. In addition, I am interested to learn what the FDA is doing to combat illegal compounding and radiological diagnostics. We need to understand what FDA's plan is for—what its plan is for enforcing current law. If the FDA feels it needs more resources, then they need to request them and they have to tell us what exactly they need. Otherwise, there is no excuse for the FDA not performing its mission.

As I listened to your testimony, Mr. Chairman, on the bulk sale of drugs here, I am concerned about what is happening on the Internet. As you know, Mr. Klink and I have been working on the On-line Pharmacy Consumer Protection Act, and we have been working with the administration to come up with a bill that can be acceptable to both sides because we feel it is a huge problem.

So now you take these counterfeit bulk drugs—and you say we know about 18 percent of them. How many more and are they being sold on the Internet? In fact, I have no reason to think they are not being sold over the Internet. I think this hearing has so much more we can explore, and I think it will be a very, very interesting hearing.

So I thank you for holding this hearing, Mr. Chairman.

Mr. Chairman, I am going to close with that, but before that, I would like to ask unanimous consent to place Mr. Dingell's statement into the record. He is currently at a meeting on the patients' bill of rights. Otherwise, he would be here, because I know Mr. Dingell is very interested in counterfeit bulk drug sales.

So with unanimous consent I would submit his statement forward, please.

Mr. UPTON. Without objection, his statement will be made a part of the record, and all members of the subcommittee's statements, in fact, will be made a part of the record.

Mr. STUPAK. I yield back the balance of my time.

Mr. UPTON. Thank you.

[The prepared statement of Hon. John D. Dingell follows:]

PREPARED STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. Chairman, I have long been concerned about counterfeit, substandard, misbranded, and adulterated drugs entering this country from abroad. Previous investigations conducted by this Subcommittee more than a decade ago ultimately led to the passage of the Prescription Drug Marketing Act, which added measures to protect consumers from potentially dangerous foreign drug sources. But protecting consumers from questionable and dangerous drug products manufactured abroad remains a formidable challenge.

I remain concerned that the Food and Drug Administration (FDA) has yet to develop a suitable framework, in the face of potentially greater risks, for protecting the public. The Agency remains alarmingly behind in foreign inspections of firms sending drug products into the United States. And it still lacks the ability to track and measure the counterfeiting problem.

The FDA is supposed to inspect firms for Current Good Manufacturing Practices (CGMPs) *before* they are approved to ship a drug product into the United States. Nevertheless, just last week FDA reported to us that approximately 4,600 foreign drug firms have shipped to the U.S., but have never been inspected by the FDA. Cause for added concern is the fact that firms in two countries with historic drug counterfeiting problems, China and India, are prominent on that list. According to FDA's records, 623 firms from China that have shipped drug product to the U.S. have never been inspected by the FDA. The figure for India is 409.

To make matters worse, the problem of tracking dubious manufacturers seems to be getting worse, not better. FDA still lacks the basic information technology to allow it to efficiently communicate with the Agency's many other databases to provide staff with mission-critical information. A workable system for tracking who sends what and *when* to this country, and whether their manufacturing practices are acceptable, should already have been implemented. Commissioner Henney should immediately determine the Agency's information technology requirements for such a system and implement the system as soon as practicable.

I also remain troubled that the FDA still lacks the ability to gather information about counterfeit, substandard, or even adulterated materials on a *real-time* basis. It is my understanding that, in recent staff discussions with the Agency, FDA officials agreed that it might be useful to require manufacturers to report immediately to the FDA if they discover any counterfeit bulk in their manufacturing processes. Currently, there is no such requirement, and that unnecessarily leaves other manufacturers and consumers at some risk. The implementation of such a requirement should allow FDA to develop a "real-time" database that could not only warn other companies if a particular product from a particular supplier is in question, but also allow the Agency to better understand and address this problem.

Mr. Chairman, I believe that drug counterfeiting is a very real problem that will likely grow worse in the future. With the introduction of now *hundreds of Internet sites* selling prescription drugs with almost no regulatory framework in place, the environment and the incentive for using fake bulk drugs, making fake drugs and selling them directly to consumers is obvious. FDA lacks a credible framework for addressing these public health risks, and that is very worrisome.

Mr. UPTON. Mr. Burr.

Mr. BURR. Thank you, Mr. Chairman.

Let me take this opportunity to welcome our colleague, Mr. Stupak, back. We have missed him, and I am sure that his participation in this will help to enlighten this issue.

Mr. Baker, let me welcome you. Let me suggest to you that the way to get started with this committee is to fulfill the requirements of the rules of the committee. Your testimony was turned in at 3 p.m. yesterday. The committee rules require those who testify to submit their testimony, I think, 48 hours in advance, so that members actually have an opportunity to read it, to study it, to understand what it is that Federal agencies are trying to do, understand, engage their level of passion and commitment to the issues.

I think you have done a very good job of trying to lay out what the scenario is at the FDA. It would have been better, quite honestly, if the Commissioner were here. I am sorry that there was a conflict and that she had a week of travel; but clearly, if she got back yesterday, she could have also submitted testimony at 3 p.m. the day before the hearing.

So I don't see that there is a tremendous amount of advantage, but I look optimistically at your testimony and the opportunity to go through some questions with you.

Let me just read one part of your statement here. You say, "It is important to distinguish between counterfeit drugs and products that are contaminated or otherwise improperly manufactured. While each of these conditions may"—may—"pose a threat to public health, counterfeiting is quite different and a much more rare occurrence in the drug manufacturing industry. The FDA Act states that a counterfeit drug," and you go into a very specific definition.

If your intent is to come here and to debate what the specific definition of counterfeit or threat is to the drug market in this country, I hope you will change before we start.

We are not here to debate definitions. We are here because, one, a problem exists; two, the FDA agrees a problem exists; three, the FDA has not done everything within its power to solve the problem. For that reason, there is an appropriate role for the Oversight and Investigation Subcommittee to play in the solution of this problem.

Let me go on in your testimony, if I can, to import alerts. Page 22, near the end, "While counterfeit drugs continue to be an issue of concern, it was determined that there was no specific need for a Commissioner's Office initiative."

That tells me that the level of concern about the issue is not as great at the end of your testimony as it was at the beginning of your testimony.

I hope that you will have an opportunity to set the record straight on what the level of commitment at the Food and Drug Administration is on solving this issue of counterfeiting or contamination, this issue of a public health question to an agency that I quite honestly have spent a tremendous amount of time trying to make sure that the gold standard that the American people expect, that the FDA employees have worked aggressively to maintain, is maintained in every piece of legislation that goes out of this institution.

I certainly hope that we will continue to do that and that you will enlighten us on what we can do legislatively to make sure that everything possible is done at the FDA to assure the safety and efficacy of everything that goes into pharmaceuticals.

Mr. Chairman, I thank you and I yield back.

Mr. UPTON. Thank you.

Mr. Bryant.

Mr. BRYANT. Thank you, Mr. Chairman.

I might first thank you for having this hearing and thank our witness, our distinguished witness, for being here today. I look forward to his testimony.

As you explained, there are many competing factors for our time, and we may be in and out a little bit during the hearing, but I do appreciate your coming today.

I think this is a good subject for a hearing and I want to commend our chairman for having this. I would echo his remarks, as well as my friend from Michigan, Mr. Stupak's remarks, as well as Mr. Burr's remarks; and would add that as I understand, in reading from some of the preparatory materials for this hearing, the issue that we are concerned with today and we would like to hear from you is: Does the use of counterfeit, unapproved bulk drugs pose a threat to the safety and efficacy of other finished drugs?

Mr. Burr sort of touched on that, and maybe what I hear him saying is his impression that the FDA does not consider this to be a significant problem. Maybe I misunderstood what he said, but I think that was his construction of what your statement says.

But if there is a legitimate threat out there, what does the FDA do in its regulatory system to ensure that that does not happen? And second, does the FDA have any initiative, anything to put forward today to us, to explain what you are doing to ensure that U.S. prescription drug supplies are free from counterfeit or unapproved bulk drugs?

I think those are the issues. Is there a problem? And if you agree there is a problem, what are you doing about it?

As I read other materials—our chairman mentioned some of the statistics that are involved here; and I know, like all agencies, or I suspect, you will plead that there are not enough people to go around and FDA needs more people to help enforce this. Nevertheless some of the statistics are mentioned here. Again our chairman has mentioned some of them already, but I will mention a couple more.

There are approximately 310 points of entry in the United States, but in fiscal year 2000, the FDA has only 68 full-time equivalents in the field allocated to human drugs. They mentioned the 4,600 foreign drug manufacturers who have never been inspected by the FDA. Only about 18 percent of the total number of foreign drug manufacturers are shipping to the U.S. at this time—in 1998, I should say—that the FDA has information on. The tracking system, foreign inspection force, does not include reports which relate to manufacturing violations with a product from a country, and so on.

These are generally admissions, I think the FDA has made in the letter to Chairman Bliley.

One final comment in regard to all of this, and I say this as a former U.S. Attorney—and I know Bart Stupak is a former law enforcement officer and probably has seen this: It is a phenomenon out there among our investigative agencies, called TURF. And I found that as a U.S. attorney, who sort of helped run investigations with the idea that we would gather facts from the FBI and the DEA and all of those investigators out there in our office and help prosecute the bad guys. But I found this concept of turf battles.

In reading through these materials, I see where the FDA—and I would like maybe to hear from you if this is true or not—the FDA has not worked with the Customs Service to investigate imported counterfeit bulk sales or bulk drugs since 1996 and does not have any ongoing criminal enforcement action or strategy, for that matter. I think this gets into something else, but again the issue of whether you are working cooperatively with other agencies that have a similar jurisdiction and a similar goal to prevent this type of conduct from happening.

Again, realizing that we don't call it turf battles, but that is what it is, I would like to know why the FDA is not working with Customs and maybe any other agency that would have, again, similar jurisdiction that would help by combining resources, and maybe even a task force or something like that, to stop this.

I guess in the end, as I close, we have got to agree, first, if there is a significant problem or not; and that is what I would like to first hear, too.

With that, I would yield back my time.

Mr. UPTON. Thank you.

[Additional statement submitted for the record follows:]

PREPARED STATEMENT OF HON. TOM BLILEY, CHAIRMAN, COMMITTEE ON COMMERCE

Mr. Chairman, this hearing is of vital importance. On June 23, 1999, at a hospital in Los Angeles, a 10-year old boy was given a dose of an antibiotic called gentamicin sulfate. After he finished getting this dose, he got unexpected side effects of chills, shaking, and 102 degree fever. The drug he took was made of ingredients that came from a bulk drug plant in China called Long March Pharmaceutical. This 10-year old boy was just one of what turned out to be 155 American patients in 1998 and 1999 who suffered from these reactions that were linked to the Long March ingredient. Some of these reactions were life-threatening. While none of the 155 patients died from these reactions, there are other patients who may have died from unknown impurities in counterfeit or substandard gentamicin. Whatever was wrong with this drug ingredient, it slipped through the FDA and the U.S. drug companies.

Could the FDA have prevented the gentamicin problem? The FDA years ago had tips about counterfeit gentamicin and had opportunities to prevent the gentamicin problem. In 1994, FDA investigated counterfeit bulk gentamicin sulfate, but dropped the investigation because the suspicious lots were no longer available. Nothing was done on the regulatory side, not even taking samples of gentamicin sulfate from various U.S. firms to test for impurities or counterfeiting. Based on a 1996 memo from one of its criminal investigators, the FDA had information from a case involving Long March-labelled counterfeit drugs for animals that told them that counterfeit gentamicin sulfate for humans was being sold in the U.S. In addition, FDA had recommendations in 1996 to deter, detect, or interdict counterfeit gentamicin sulfate and other counterfeit bulk drugs. Many of these key recommendations were not implemented. Lack of FDA action left American patients vulnerable to imported bulk drugs like the Long March gentamicin.

The FDA's record on controlling counterfeit bulk drugs so far is a record of failure. That is an outrage. As far back as 1991, the FDA had evidence from its field force that suggested widespread availability of counterfeit bulk drugs in both human and animal drug industries. In 1996, then-FDA Commissioner David Kessler established a counterfeit bulk drug initiative and a working group to deal with this issue. A year later, the FDA disbanded the Commissioner's working group and downgraded the priority of counterfeit bulk drugs. Since the FDA has downgraded the priority of counterfeit bulk drugs, international authorities including the World Health Organization (WHO) last month have recognized the growing problem of counterfeit drugs. While the FDA has taken some small steps in improving some of its systems, much remains to be done.

As the Committee's investigation has revealed, the FDA's regulatory system used to protect Americans from counterfeit or substandard drug ingredients has significant holes. For example, many times FDA will allow drug products into our country not based on proof of authenticity, but merely on the representations of an international broker, who could in fact be the counterfeiter. FDA has only partial information, if that, on the original source to determine authenticity. The FDA's own people acknowledge that the import alert system is broken and that using drug listings for admitting drug imports has had a dismal record. The FDA admits it has information on only 18 percent of the foreign drug manufacturers shipping to the U.S. The FDA admits there are about 4,600 foreign drug manufacturers that have shipped to the U.S. since October 1997 but have never been inspected by the FDA, including 623 in China and 409 in India. At the time of entry at the ports, the inspectors do not have the ability to know where the drug shipment is going in the U.S. and what will really happen to it.

What has been truly disappointing has been FDA's apparent lack of interest in using the authority and resources the Congress gave the FDA specifically to investigate counterfeit bulk drugs. In 1993 the FDA's Office of Criminal Investigations was created specifically to give the FDA the capability to investigate counterfeit drugs. By statute, FDA has special enforcement powers related to investigating counterfeit drugs.

But what has been the record? How has the FDA used this authority? In May 1996, one of FDA's criminal investigators wrote a memorandum to his supervisors at the FDA's Office of Criminal Investigations about evidence from a criminal investigation showing the threat of counterfeit bulk drugs imported into the USA. But his supervisors did nothing to follow-up on the investigative leads or to implement or suggest improvements in criminal investigations of counterfeit bulks. In its June 2, 2000 letter to me, the FDA admits in the area of counterfeit bulk drugs the Office of Criminal Investigations has no open investigations, has not initiated even one investigation, and has not worked with any other federal agency investigating counterfeit bulk drugs. There is no criminal investigative strategy included in the FDA's draft 1999 Work Plan on counterfeit drugs. None.

Ladies and gentlemen, bulk-drug counterfeiting and the acts that perpetuate the fraud are federal crimes. These crimes threaten the public health and the integrity of the pharmaceutical industry, place law-abiding bulk suppliers at a competitive disadvantage, and victimize U.S. drug companies. Just last month, the WHO, international pharmacists, and international drug manufacturers issued public statements about the major problem of drug counterfeiting. It seems that imported drug counterfeits are increasingly recognized as a major problem.

In some of its statements to the Committee, the FDA assumes there must be no major problem even though it has not conducted a public health assessment of the counterfeit bulk drug issue and has little quantifiable information on the subject. However, the FDA told Committee staff that they had learned from an investigation about 10 years ago that Americans had died from counterfeit bulk antiseizure medicine. The FDA told staff as well that there are public health concerns with introducing counterfeit and unapproved bulk drugs into our medicines. This is why FDA has in place regulations and inspections to deal with bulk drug ingredients.

Mr. UPTON. Our witness today is Dennis Baker, Associate Commissioner for Regulatory Affairs at the Food and Drug Administration.

Mr. Baker, welcome. As you know, we have a long-standing tradition of taking testimony under oath. Do you have any objection to that?

Mr. BAKER. None whatsoever, sir.

Mr. UPTON. Committee rules also allow you to have counsel, if you wish to have counsel represent you as well.

Do you wish to have counsel?

Mr. BAKER. No, I do not.

Mr. UPTON. If you would stand and raise your right hand.

[Witness sworn.]

Mr. UPTON. You are now under oath and your testimony is made a part of the record in its entirety, and the time is yours. Thank you.

TESTIMONY OF DENNIS BAKER, ASSOCIATE COMMISSIONER FOR REGULATORY AFFAIRS, U.S. FOOD AND DRUG ADMINISTRATION

Mr. BAKER. Thank you, Mr. Chairman, and good morning, Mr. Chairman, and members of the committee.

I am Dennis Baker, Associate Commissioner for Regulatory Affairs at the U.S. Food and Drug Administration.

Mr. UPTON. If you could just put the mike a little closer.

Mr. BAKER. Is that better?

Mr. UPTON. That's better.

Mr. BAKER. Thank you.

With me today, I have Mr. John Taylor. He is Acting Director of our Office of Compliance at the Center for Drug Evaluation and Research within FDA. Together, our offices are responsible for regulating the importation of foreign drugs.

I appreciate this opportunity. I am rather new to FDA. I have been on board about a year now. I came on board from the State of Texas, so I have had some eye-opening experiences, as you might guess, and coming here today is another eye-opening experience.

But what we are here today about is imported counterfeit bulk drugs, and the Agency's actions to protect the American public from the risks of those drugs.

I want to preface my remarks by noting that while we take very seriously the counterfeiting of drug products, we still believe the overall quality of drug products in the country to be very high. The public, we think, can be confident that the drug products they use are safe and effective.

Although FDA takes many steps to protect American consumers and patients against unsafe drugs, we recognize that more can be done and should be done. There is room for improvement in our abilities both to quantify the potential for the entry of counterfeit bulk into the U.S. market and, when warranted, to strengthen our regulatory or enforcement activity.

In this testimony, I will highlight FDA's efforts to ensure that imported bulk drugs meet the requirements of the Food, Drug and Cosmetic Act. More detail on FDA's programs and activities in this area is provided in my written statement, and I request that it be included in the record.

Mr. UPTON. Yes.

Mr. BAKER. Simply put, the Food, Drug and Cosmetic Act defines a counterfeit drug, as we mentioned earlier, as a drug that bears a false identification of its manufacturer, processor, packer or distributor. The definition applies to active pharmaceutical ingredients, APIs, as well as finished dosage forms that are deliberately and fraudulently mislabeled or misbranded with respect to their identity and source.

Counterfeit APIs pose a real or potential health hazard because their manufacturer is often unknown, which makes it impossible to establish an accurate product history.

As a result, the safety, quality and efficacy of the product cannot be assured. Central to FDA's system of protection for the integrity of prescription and nonprescription drugs are the standards for safety and effectiveness in manufacturing that are established by the Center for Drug Evaluation and Research.

It is important to note that a key element of this system of protection is the responsibility that a drug manufacturer has to test and validate the safety, purity and consistency of the APIs it uses in the manufacture of its products.

Some of the strategies employed by FDA to maintain these standards include the rigorous scientific evaluation of all marketing applications for new innovator and generic drug products and monitoring the quality of APIs in finished dosage forms manufactured in and imported into the United States; collecting and evaluating information on adverse events associated with marketed products; and conducting inspections to ensure that manufacturers produce high-quality pharmaceutical products.

Over the last decade, FDA has taken a close look at the issue of counterfeiting, and we have engaged in wide-ranging discussions on whether our regulatory enforcement programs were up to the task or needed reworking.

Let me emphasize that many of our discussions in the earlier part of the decade were based on the fact that our information resources were far less capable than what we have today. Although there is still room for improvement, and I would say much improvement, most of the information systems in use today were established during the 1990's in response to our need for better information.

The task before us now is to better integrate the various information resources into a unified environment, a unified information technology (IT) environment. We fully recognize that we have been working from a collection of independently developed data bases, all of which contain critical information, but they clearly need to be integrated; they have to be linked. This unified environment will make better information available to the field, where we must make quick decisions on the admissibility of products, and it will allow us to reconcile the data now contained in our various existing systems.

We have a program of technology upgrades in place. Those upgrades have already resulted in the roll-out of the FACTS system which incorporates data from the OASIS import registry and the COMSTAT compliance information system.

In an effort to begin to address the weakness in IT available to import inspectors, a pilot was initiated in the Philadelphia district to provide import inspectors with access to CDER's EES system, which tracks drug applications. This allows the import inspectors to increase the probability of confirming authentic sources of APIs. The goal is to ultimately have access to a single data base that includes all the information needed and houses a true foreign establishment inventory.

The FDA has also restructured its foreign inspection program in order to better target those firms and products that have the most potential for problems, including counterfeiting.

While the bulk of our foreign plant inspections are still in support of new drug applications, we have instituted a tiered inspection system based on potential risk to the consumer. In spite of our best strategies, however, resource limitations will prevent us from conducting universal foreign drug inspections.

Now, that being said, could we do a better job with the resources we have? Certainly.

FDA has also revised the sampling of products under the drug product surveillance program, and these samples are analyzed by our Forensic Chemistry Center. Since 1998 we have been focusing on collecting a greater number of samples of targeted APIs to determine if a product is authentic and meets specifications. Building this data base for API information will be helpful to our field inspectors in identifying possible counterfeit APIs. Currently, this data base contains information on approximately 400 to 500 APIs.

Another aspect of our program emphasizes a stronger cooperative effort with foreign governments and industry.

Mr. Chairman, FDA is alert to the fact that our protections against counterfeit drugs are in need of improvement. Building and maintaining a strong regulatory framework and providing the tools to ensure the integrity of imports is a complex and resource-intensive undertaking that requires flexibility in response to the constant growth and changes of the global market.

While our agency has done much in recent years to meet these demands, clearly more can be done. Today, I would like to announce five additional new initiatives we are undertaking to further improve this system. Just last January, I allocated funds to the Forensic Chemistry Center for analytical work in assessment of APIs gathered through targeted inspections of importers. The FCC API data base will be made available electronically to all field inspectors by January 2001.

While the Philadelphia pilot does not fix the entire IT problem, in the interim, it clearly provides a benefit to our field force. By the end of the year, we will expand this pilot nationwide so all of our field force has access to the EES data, a real-time reading of the data.

Exporters to the U.S. are required by FDA to provide the name of the foreign manufacturer upon entry to the U.S. This information has been inconsistently provided by importers and the agency has not enforced this requirement. Effective immediately, we are going to put all importers on notice that this information must be accurately provided and the entry of their products into the U.S. will be contingent upon it.

At the suggestion of Mr. Dingell and Mr. Klink, we considered requiring domestic manufacturers to provide information to FDA when they discover that bulk materials they receive are substandard, ineffective or appear not to be from the approved source. We did consider this idea. We believe it will provide us with useful information, and we are looking at regulatory approaches for implementing this requirement.

A vigorous and effective system requires sufficient resources that provide the necessary expertise, scientific methodologies, tools for testing and integrated information systems. We are committed to ensure the Agency has what it needs. We look forward to working further with the committee as we strive to provide the American public with the protections it expects and deserves.

This concludes my testimony, and we will be happy to answer any questions you may have.

[The prepared statement of Dennis E. Baker follows:]

PREPARED STATEMENT OF DENNIS E. BAKER, ASSOCIATE COMMISSIONER FOR REGULATORY AFFAIRS, FOOD AND DRUG ADMINISTRATION

Good morning, Mr. Chairman, and Members of the Committee. I am Dennis E. Baker, Associate Commissioner for Regulatory Affairs (ACRA) at the United States (U.S.) Food and Drug Administration (FDA or the Agency). With me today is my colleague, John M. Taylor, Acting Director, Office of Compliance, Center for Drug Evaluation and Research (CDER). I am pleased to come before the Committee to discuss your concerns about imported counterfeit bulk drugs and the Agency's actions designed to protect the American public from the possible risks that such drugs may pose.

It is important to note that the overall quality of drug products in this country is very high. However, FDA takes very seriously allegations regarding the counterfeiting or adulteration of drug products. We recognize that more can be done to quantify the scope of the problem counterfeit bulk drugs may pose in the U.S. market, and strengthen our regulatory or enforcement activity, when warranted. In this testimony, I will describe efforts the Agency has taken to ensure that imported bulk drugs meet the requirements of the Federal Food, Drug, and Cosmetic (FD&C) Act. "Bulk drugs" are active or inactive ingredients used in the manufacture of finished dosage drug products. While safety issues clearly apply to all products that are classified as bulk drugs, at the Committee's request, this testimony will generally focus on issues related to the importation from foreign sources of active pharmaceutical ingredients (APIs), which was the subject of Chairman Bliley's May 8, 2000, letter to the Agency.

It is important to distinguish between counterfeit drug products and products that are contaminated or otherwise improperly manufactured. While each of these conditions may pose a threat to public health, counterfeiting is a quite different, and much more rare, occurrence in the drug manufacturing industry. The FD&C Act states that a counterfeit drug is:

> "A drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor."

More simply stated, a drug that identifies itself as the product of a drug manufacturer, processor, packer, or distributor other than the actual manufacturer, processor, packer, or distributor of such drug is counterfeit under the FD&C Act. This definition applies to active pharmaceutical ingredients, intermediate pharmaceuticals, and finished dosage forms that are deliberately and fraudulently mislabeled or misbranded with respect to their identity and source. Counterfeiting can apply to innovator or generic products.

Counterfeit APIs pose a real or potential health hazard because their manufacturer is often unknown. The fact that the manufacturer is unknown means that there is no product history. Therefore, the safety and efficacy of the product cannot be assured, the impurity profile is unknown and the age, storage, manufacturing environment, and/or the synthesis of the product cannot be determined. Moreover, the failure to have a product history means that the results of research and development and the clinical trials done by legitimate pharmaceutical product manufacturers are negated.

The participants in illegal counterfeiting activity may include manufacturers of API pharmaceuticals, manufacturers and repackers who relabel and substitute API products in the distribution chain, importers, brokers, domestic agents, and purchasing agents either acting alone or in concert with a corporate unit. There are certain products that especially lend themselves to counterfeiting. In general, very expensive chemicals that are purchased in small quantities or less expensive chemicals that are purchased in very large quantities are particularly vulnerable to counterfeiting.

I. THE REGULATION OF ACTIVE PHARMACEUTICAL INGREDIENTS

FDA is responsible for the safety and quality of domestic and imported pharmaceutical products. Specifically, FDA's CDER establishes standards for the safety, effectiveness and manufacture of prescription and over-the-counter (OTC) drugs. In addition, FDA's human drug program applies premarket review, postmarket surveillance, education, research and other strategies to ensure that all drug products are safe and effective and that information on the proper uses of the drug products is available to all users.

The strategies employed by FDA include:

- regulating the testing of investigational new drugs (INDs);
- evaluating the data in new drug applications (NDAs) for marketing new drugs and abbreviated new drug applications (ANDAs) for marketing generic drugs;
- monitoring the quality of API and finished dosage drug products manufactured in and imported into the U.S. through post market surveillance programs;
- collecting and evaluating information on adverse effects associated with the use of marketed products;
- regulating the advertising and promotion of prescription drugs;
- establishing and monitoring standards for use, labeling and composition of both prescription and OTC drugs;
- conducting inspections to ensure that manufacturers produce safe, pure and high quality pharmaceutical products; and
- evaluating the conditions under which drugs are manufactured, packed, tested and held.

FDA's human drug program also disseminates timely and accurate product information to the medical community and the public regarding new drugs and their uses, identifies drugs with the potential for abuse, and makes recommendations to the Drug Enforcement Administration (DEA) for drug classification and control.

Foreign manufactured drugs imported into the U. S.—both bulk and finished products—fit into the Agency's regulatory framework through new and generic drug evaluations, drug quality assurance, inspections, postmarketing surveillance and adverse drug event reporting programs.

New Drug Evaluation/Generic Drug Evaluation

The goal of the new and generic drug approval process is to ensure that 1) new drugs brought to market are safe and effective as labeled for their intended use, and 2) generic drugs approved for marketing are safe, effective, and manufactured in a way that ensures their continued safety, efficacy, and bioequivalence. Personnel from the Office of Regulatory Affairs (ORA), sometimes accompanied by chemistry or other professional staff from CDER, conduct pre-approval and post-approval inspections of the facilities manufacturing drug products that are identified by drug sponsors in their applications.

FDA's Pre-approval Inspections Program (PAI) provides for the investigator to verify the accuracy and authenticity of data submitted by firms in support of the approval of their new or abbreviated new drug applications and to assess the firm's compliance with current good manufacturing practices (cGMP). The program covers both domestic and foreign manufacturers of both finished dosage form products and APIs.

A drug manufacturer is responsible for testing and validating the safety, purity and consistency of the APIs it uses in the manufacture of its products. In fact, all such manufacturers are required to disclose the source of their APIs in their applications, and both domestic and foreign API manufacturers must be in compliance with cGMPs prior to the approval of those applications. Drug Master Files (DMFs) are established to allow producers of active ingredients and other formulation materials to submit confidential commercial information directly to FDA. Therefore, these bulk drug inspections are considered to be pre-approval inspections and include inspectional verification of the information submitted to the DMF by the bulk drug manufacturer. The DMF contains manufacturing information pertinent to the formulation material. It is referenced by an applicant for a finished dosage form and is considered part of the application.

Foreign and domestic bulk manufacturers are reevaluated periodically for cGMP compliance, either during pre-approval inspections for a different product, or by a routine drug process cGMP inspection under the API program.

Drug Quality Assurance Program

Without proper process validation and control, marketed drugs may be deficient in many ways such as being subpotent, superpotent, or contaminated with other drugs or microorganisms. CDER is responsible for conducting postmarketing assurance monitoring of the overall manufacturing quality of drugs and maintaining drug establishment registration and drug products listing. In conjunction with ORA, CDER must also ensure that the manufacturing, processing, packing, and holding of drugs are such that the highest quality products will be marketed.

FDA inspections and product analyses are conducted to ensure that firms are validating their manufacturing processes. Comprehensive cGMP evaluations of drug products or dosage form are conducted. These inspections include domestic and foreign API and finished dosage form manufacturers.

In addition, CDER initiates drug sampling surveys that involve the collection and analysis of imported bulk drug substances and finished products that are then analyzed by Agency field labs for quality and forensic laboratories for evidence of counterfeiting. Selection of drug products for FDA sampling and testing under the Drug Product Survey Program is based on the following criteria: therapeutic significance; emerging problems; impurities; stability concerns; results of previous drug surveys; economic importance; and compliance history of the firm. Foreign active pharmaceutical ingredients have been added as sampling/testing targets. CDER strives to obtain voluntary support from the pharmaceutical industry whenever possible, informing firms of problems with their products or manufacturing processes so that correction may be made as expeditiously as possible, but takes regulatory action when necessary to effect the required changes.

Postmarketing Surveillance and Epidemiology

FDA employs other surveillance programs, including drug listing review of imports and the Drug Quality Reporting System under MedWatch. ORA is establishing a library of authentic bulk drug substances to use in investigations to identify counterfeit drugs.

II. FOREIGN INSPECTION WORKING GROUP

The continuing increase in international trade has turned the world into a global marketplace. The number of API and finished drug products manufactured abroad for the U.S. market is growing. It has been reported that as much as 80 percent of the APIs used to manufacture and produce prescription drugs in this country is imported from other countries. Therefore, over the last decade, FDA has substantially increased its worldwide inspectional and import monitoring operations, but the rapid expansion of the world market will continue to challenge our ability to direct appropriate levels of resources and operations to the foreign arena. FDA must continually recalculate its enforcement tools to ensure that the American public is protected from adulterated and unsafe products entering the U.S. market.

To keep pace, FDA has stepped up its inspectional and import-monitoring activities since the early 1990s, however, the Agency recognized that it needed to do more. In 1995, the FDA formed a Foreign Inspection Working Group (FIWG), comprised of representatives from all parts of the Agency, in an effort to evaluate the Agency's current foreign inspection program and related import product monitoring. The working group devoted months to understanding and identifying FDA's strengths and weaknesses in its foreign inspection program. The FIWG issued a summary report in June 1997. This evaluation cuts across Agency program areas, however, I will focus on the drug program and how it relates to bulk drugs, the findings, and the Agency's subsequent actions over the past three years.

Inspection Planning

Prior to Fiscal Year (FY) 1997, FDA's foreign inspection program in large part focused on pre-approval inspections. In the early 1990s, foreign inspections resulted in a higher percentage of foreign manufacturers with significant GMP problems relative to domestic facilities. These findings indicated a need for more post-approval surveillance coverage to help assure that imported drug products are produced in accordance with cGMPs.

CDER addressed this issue by structuring its foreign post-approval inspection scheduling using a risk-based strategy that allows it to more effectively utilize limited resources. Specifically, assignments are still primarily application driven, in that all foreign inspections of firms that are part of an application are conducted during the course of the application review. Additional post-marketing surveillance inspections are scheduled based on risk as assigned by a four-tiered system:

- Tier 1—firms needing reinspection due to a previous finding of "official action indicated";
- Tier II—firms manufacturing sterile bulk or finished dosage products;
- Tier III—firms with a higher number of applications and firms manufacturing bulk drugs for use in injectable dosage forms; and
- Tier IV—all other firms.

The tiered system has had the beneficial effect of focusing our limited resources on the firms that pose the highest risk to the American consumer. We have maintained a level of inspecting about 250 foreign firms per year for cGMP compliance and pre-approval acceptance. The inspections performed have been in the Tier I and Tier II categories.

The negative consequence, however, is that by continually emphasizing these high-risk firms we are not able to get to the Tier III and Tier IV firms, thereby lengthening the gap between inspections. CDER has recognized this problem and has identified and provided to ORA a priority list of 24 firms in China and 32 firms in India that have not been inspected but, according to the Operational and Administrative System for Import Support (OASIS) data, have shipped product in the last two years into the U.S. ORA is working these firms into inspection planning as resources permit and travel plans make opportunities available. For example, inspections of these priority firms can be added to pre-approval inspection trips.

Official Establishment Inventory

The Agency's Official Establishment Inventory (OEI) is a compilation of firms FDA has inspected, firms that have shipped products to the U.S., as indicated by the OASIS database, and firms that have listed as part of the Agency's drug listing program. FDA has completed evaluations of entry data from OASIS and is using this information to supplement the inventory of firms in the OEI. This is an ongoing process. FDA recognizes that there are weaknesses in this data, due in part to the fact that the OASIS system is user-driven. The Agency is using broker evaluations in part to increase the integrity of the submitted data and eventually included in the OEI.

The Agency is hindered by not having a complete list of foreign facilities manufacturing drug products for the U.S. market. This finding indicates a need to improve the Agency's information database on foreign firms exporting drug products to the U.S. The Food and Drug Administration Modernization Act (FDAMA) of 1997, requires the registration of foreign establishments. Once we have completed the rulemaking process and put the technology in place to implement this requirement, the Agency will have available to it a comprehensive listing of foreign establishments exporting drugs to the U.S.

Having a complete OEI, however, is only one step. We also must have the information technology to be able to more fully utilize the data we already have to the Agency's benefit. Therefore, FDA has begun a process of upgrading its hardware and software systems to move beyond the fragmented and independent systems of the past into an integrated information environment where data is more readily available and more easily manipulated to provide information and analyses that has not been possible before.

The Agency recognizes while we have made great strides in improving our information technology, we still do not have systems that can effectively and efficiently communicate across the Agency, or readily provide field staff with critical information they need.

FDA is implementing the upgrade of our information technology systems to utilize wide area network (WAN) technology, which will support the availability of much more information to inspection officers. We are evaluating both the technology, as well as the cost, or further integrating our various sources of data into unified databases.

The OASIS system uses information input by filers (Custom House Brokers and importing firms) to facilitate the screening and/or inspection of imported products that are subject to FDA regulation. OASIS began as a pilot program in the Seattle District in 1992. It interfaced with the U.S. Customs Service Automated Commercial

System (ACS), screened entries (using ACS) and provided the initial operational support to FDA users. The interface with ACS and the screening subset of the system (known as EEPS) was implemented nationally by June 1995, and use of the OASIS system by industry became mandatory in December 1996. The baseline of the current version of OASIS with full basic operational functionality was implemented nationally by October 1997. The system has undergone continuous improvement of operational support. A major change in September 1999, moved screening from ACS to OASIS and expanded screening to cover all data elements.

As a user-driven system, OASIS depends upon import brokers to provide complete and accurate information. While the OASIS system provides the majority of the information it was designed to provide, it only contains 2 years worth of data, and does not electronically interface with other systems which contain additional information which would be of value to our field staff.

One of FDA's major upgrades in information technology is the establishment over the last year of the Field Accomplishment and Tracking System (FACTS), which performs a number of functions, including the ability to request, manage and report on inspections and other field assignments such as sample collections and analyses, and compliance cases. FACTS incorporates data from the Compliance Status Information System (COMSTAT) system, described below, as well as OASIS, and will eventually provide the resident environment for the foreign OEI. We also are actively working on integrating the Establishment Evaluation System (EES), which provides information on inspection requests and outcomes to compliance officers, drug reviewers and field personnel, with the FACTS database.

COMSTAT provides the compliance status of foreign manufacturers based on the results of cGMP inspections. COMSTAT data is shared with other Federal agencies and foreign inspectorates to ensure that pharmaceutical products purchased or cleared for import meet acceptable standards. Ideally, this data should be readily available to FDA's import inspectors making admissibility decisions. COMSTAT does not include the drug listing identification number FDA assigns to each manufacturer in the Drug Listing database, which lists the products of drug firms registered with CDER. FDA is pursuing the linkage of information in the Drug Listing database with COMSTAT so that we can easily match foreign manufacturers who have "listed" with their compliance status. The Drug Listing database also does not interface with OASIS, which would assist import officers by automatically comparing manufacturers and listed pharmaceutical products to products offered for importation, and this is another area where we are working on establishing a linkage.

Finally, we are also actively working on connecting the current EES with the import data available in OASIS, as described more fully later with regard to a pilot project in our Philadelphia District.

Import Alerts

FDA has identified the need to establish enhanced procedures to better assure that an import alert notice for a product or company will, in fact, prevent the violative products from reaching the U.S. consumer. We have begun this process by making import alerts available to interested parties on FDA's Internet site.

International Information Exchange

The Agency needs to strengthen and improve communication with the public health and regulatory components of foreign governments. FDA foreign inspections are "pre-announced," because FDA must obtain permission to enter the foreign country. Therefore, it is difficult for FDA to assure that the firm is operating under normal conditions during the inspection.

Establishing strong relationships with the foreign governments will facilitate both access to the country and a fair and frank exchange of information regarding the regulatory status of facilities in that country. The Agency has negotiated a Mutual Recognition Agreement (MRA) with the European Union. This agreement involves an upfront investment of resources on the part of FDA that should result in expanded inspectional coverage of foreign firms by foreign inspectional body counterparts. On a parallel track, FDA has a number of Memoranda of Understanding (MOUs) with foreign countries to obtain inspectional information that will supplement what FDA is already doing.

Sampling

Evidence of product quality problems has not been identified during current surveillance sampling activity. We will continue to target high-risk drug products for sampling.

III. COUNTERFEIT DRUG INITIATIVE

In 1995, the Agency began a closer examination of the issue of counterfeit drugs. For just over 2 years a cross-cutting group reviewed both the Agency's knowledge of the extent of counterfeiting and the adequacy of the systems in place to handle it when it occurred. While the work of this group is certainly related to the work of the FIWG as described above, the findings and observations were specific to counterfeit drugs.

Meetings with Representatives from Foreign Governments and Industry

The Agency has and continues to strengthen its international collaborative efforts with other inspectorates outside the MRA process. We have given priority to Canada, Australia, and Mexico for more development and have worked with Latin American countries on educational efforts, for example, the University of Puerto Rico project. These efforts also include a semiannual scientific exchange meeting with representatives from the United Kingdom, Germany, Canada, Australia, and the Netherlands.

The Agency has met with pharmaceutical industry representatives from innovator and generic drug companies to discuss the importance of sharing information that they may have regarding counterfeit drug products. Discussions are held regarding the most productive ways to enhance cooperation by exchanging information and providing assistance during future investigations. Companies that produce high demand products that tend to be counterfeited often do not elaborate on the actions they are taking to combat the counterfeiting problem. While such secrecy is understandable, sharing such information would create efficiencies for both the Agency and the industry in efforts to combat counterfeiting.

In addition, in 1997, the Office of Criminal Investigations (OCI) began to coordinate international efforts aimed at identifying, investigating, and prosecuting pharmaceutical crime through liaison with international efforts that had been formed by the Forensic Chemistry Center. In 1998, OCI formally established a liaison with its international counterparts within the Medicines Control Agency (MCA) in the United Kingdom, and the German National Police, Bundeskriminalamt (BKA). This collaborative effort of sharing criminal intelligence has now grown into the Permanent Forum on International Pharmaceutical Crime (PFIFC). This working group is an international enforcement forum aimed at exchanging intelligence and ideas to foster mutual cooperation in combating pharmaceutical crime. The following countries have representatives on this forum: USA, United Kingdom, the Republic of Ireland, Northern Ireland, Spain, Germany, Canada, Singapore, Brazil, Belgium, South Africa, the World Health Organization, and the World Customs Organization. The PFIPC meets once a year and facilitates ongoing dialogue among member nations throughout the year.

Postmarket Sampling of Imported Products

As we noted above, a key element of post-marketing surveillance is the Drug Product Surveillance program. While this program provides the Agency with valuable information about the quality of drugs marketed in this country through sampling and analysis of imported and domestic drug products, the volume of imports dictates that only a small fraction of the entries are examined.

That said, there is concern that the current sampling strategy is not using the Agency's resources most effectively. Increased sampling and testing of foreign produced bulk pharmaceutical chemicals and finished dosage forms have revealed very few problems. Two changes have been made to our sampling strategy as a means to address these concerns.

1. The sampling of APIs for analysis by the Forensic Chemistry Center (FCC) to detect counterfeits was revised in 1998. The sampling now calls for the collection of five batches per year for each of the last 5 years (25 samples total) for each source of API at each finished dosage manufacturer. In the past, we received a few samples each of a large number of different drugs that was a kind of "shotgun" approach, hoping for a random hit. The new program is more focused and more likely to detect counterfeits, however, of necessity, only a few drugs can be addressed each year. Three drugs were selected for sampling in FY 1998, five drugs were selected for FY 1999, and three are targeted for FY 2000.
2. CDER's compliance program now directs FDA investigators as part of its inspection assignment at a foreign API manufacturer to ask the manufacturer to provide the FCC authentic samples of its APIs, labeling, certificates of analysis, container information, batch numbering information, size, and amounts of API produced and shipped to the U.S. The authentic information is entered into the API database and used for comparison to suspect samples.

Increased Training for FDA Import Inspectors

FDA inspectors and investigators need accessible information to help them determine the authenticity of pharmaceutical products. The Agency recognizes the need to provide training to investigators and inspectors on conducting effective API inspections while providing specific information on issues involving counterfeit and unapproved sources of drugs as well as poor cGMP compliance. Intensive training sessions will be conducted in July 2000, with U.S. Customs Service officers collaborating with FDA to provide the training. These sessions will focus on U.S. Customs Service laws and regulations, enforcement techniques that can be used at U.S. ports of entry, and a U.S. Customs Service strategic problem solving-program that targets willful violators. While not totally focused on bulk drug imports, this additional training will be highly applicable to field activity in this area.

Drug Listing

The Drug Registration and Listing System provides information on foreign pharmaceutical manufacturers, based on the statutory requirement that they list the drug products that they ship into the U.S. However, anyone can obtain a drug labeler code and therefore submit a drug listing form. The drug listing does not ensure that authentic sources or authentic material as described in NDAs is in fact being offered for admission.

To begin to address the weaknesses in the current system, a pilot program was initiated in the Philadelphia District to provide import inspectors with access to additional databases. Using CDER's EES, which tracks drug applications, inspectors increase the probability of confirming authentic sourcing of APIs. The pilot was set-up in cooperation with CDER, who donated a stand-alone computer to provide the import inspector access to the EES and IND databases and other inspection databases. The system allows inspectors to retrieve additional important data in about three to four minutes on any API entry.

The Philadelphia District Office is a relatively small API importing area compared to New York or Los Angeles. Nonetheless, this pilot has enabled Philadelphia to verify information on API entries on-line, and has resulted in approximately 50 less telephone calls to CDER seeking this information. Based on the success of this pilot program, the Agency is planning to expand this pilot program in stages until it provides nationwide EES access to all import inspectors.

Enhancing Analytical and Forensic Methodology to Analyze APIs

It has been observed that counterfeiters are becoming more sophisticated with respect to the counterfeiting of labeling, containers, seals, and documents. Therefore, to detect counterfeit APIs it will be necessary to conduct forensic analysis of the API.

The FCC continues to improve its ability to detect counterfeit APIs by enhancing its expertise, forensic methodologies, and instrumentation. Numerous APIs have been collected and chemically fingerprinted. Last year, based in part on these types of analyses, special targeted inspections were conducted in China, which resulted in one firm being placed on import alert and warning letters being issued to two others.

Develop a Strategy for Inspection of U.S. Import Agents and Brokers

The Agency is currently inspecting these facilities on a "for cause" basis in response to leads it receives about specific importers. A proposal to begin inspecting these facilities on a routine basis is in the FY 2001 workplan.

In addition, FDA has already established a broker/filer evaluation program to audit the integrity of data submitted by customs brokers. These programs have encouraged import filer compliance, and FDA is hopeful that planned enhancements to these programs will provide additional intelligence and subsequently increase enforcement actions in the areas of counterfeit and unapproved drugs.

Targeted Collection and Testing of Selected Imported APIs

As described above in the discussion of FIWG actions, despite increased sampling and testing of foreign produced bulk pharmaceutical chemicals and finished dosage forms, very few problems have been detected. Changes have been made to our sampling strategy as a means to address these concerns.

Import Alerts

The sheer volume of imported products precludes the Agency from physically examining every entry into the U. S. Therefore, other tools must be used to help control the entry of products where historical data suggests products are likely to be violative. One approach the Agency has taken is to use Import Alerts as a means to disseminate information to interested parties regarding problems with imported products. Import alerts have been made available on FDA's website. These alerts can be used to identify problem commodities, problem shippers, or problem importers, in addition to providing guidance for import coverage. An alert may cover an individual manufacturer, supplier or a particular product from an entire country. As a follow-up to an inspection, import alerts may also issue where it is determined that a manufacturer is in violation of cGMPs and the firm's status is determined to require ceasing distribution in the U. S. These products can be detained without physical examination or analysis because there is a violation of the FD&C Act.

The counterfeit drug initiative working group was disbanded last year. While counterfeit drugs continue to be an issue of concern, it was determined there was no specific need for a Commissioner's Office initiative and that ORA and the Centers are the appropriate components to manage the potential for counterfeit products as part of their on-going workload.

Challenges

Building and maintaining a strong the regulatory framework and tools to address the entries from foreign countries is complex, and the Agency needs to have the flexibility to change as the global market changes. A healthy regulatory and enforcement system requires significant staff and resources, staff expertise, scientific methodologies and the tools to conduct testing, information systems, and access to information via established networks with both other countries and the industry.

While FDA has done much in the past few years to address both the general challenges in having a strong and viable foreign inspection program and the specific tools needed to combat counterfeit drugs, clearly more can be done. We look forward to working with you as we continue to strive to provide the protection the American public expects and deserves.

I would be happy to answer any questions you might have.

Mr. UPTON. Well, thank you. As you may know, we are now going to have questions, and I am going to try to keep strict time with our questions. I am sure we will do a couple of rounds, 5 minutes apiece, and we will alternate between sides, Republican and Democrat. The clock is now running.

As you talked about in your statement—I guess the thing that grabbed me the most in your statement was that a number of us in the Congress, particularly this committee, have asked for more action taken. It seems as though a basic instinct would be that if, in fact, one of our domestic pharmaceutical industries, if they actually came upon tainted compounds coming into the country, that the first, the very first thing that you all ought to be required to do is to, in fact, go after the source, inspect it and take corrective action, whatever it may be, so that it never happens again.

Admittedly, the task is large: thousands of companies around the world sending tons of stuff into this country, without even an inspector, at virtually every port; the documentation coming in so that you don't even know necessarily that it is going to a pharmaceutical company, but instead it is a supplier—it is a middleman, it is going to some warehouse and not necessarily being traced beyond that.

But your statement at the end, that Mr. Dingell and Mr. Klink—and I would add Mr. Upton and Mr. Burr and Mr. Bliley and others—would think that one of your first requirements would be that if one of those pharmaceutical companies identified a bad supply coming in, you ought to have the requirement to be notified so that you can go find the source.

Now, that's been out there for, what, a year? Why wouldn't that be an immediate source of review, particularly in light of your comment today, which I have a copy of, which you probably read in the Wall Street Journal. It says the FDA was taken aback by numbers; the Commerce Committee had specifically asked the Agency to check its computer records for the number of foreign drug manufacturers that hadn't been inspected. When the answer came back as 4,600, FDA officials conceded that they were surprised, and then you are quoted as saying, "Surprised is probably an understatement. Concerned, definitely, and we are on it."

Well, if you are on it, you should make it incumbent upon our manufacturers to say they have got some bad stuff, can you do something about it. Yet you haven't even taken up the first step, marching down the field, of saying you have got a requirement to tell us where it is coming from.

Knowing that your staff is limited to do inspections in other countries—and, you know, you look at the numbers that I cited in my testimony, India and China and other places as well; and we showed documents of bad things happening—why isn't that the first thing that would come to your mind?

Mr. BAKER. It is difficult to explain why that wouldn't come to mind. It probably is because we look at the overall bulk product from the standpoint of contaminants and so forth: Is there some reason for rejection by the manufacturer other than counterfeiting?

Mr. UPTON. That ought to be your first line of defense. If Merck or Pharmacia—Upjohn or any major company, with all the different things that they do and they are certainly committed toward safety from top to bottom, they ought to be your front-line defense in terms of what is going on. To not even require them to notify you when something comes in—you know, the pictures that I showed earlier on of the counterfeit supply and the one that's traditional.

Let's say that was an epilepsy drug and one of them works and one of them doesn't. One of them is going to an individual who will have a seizure and perhaps die and the other one is going to be okay. I mean, these are life-and-death decisions, and we have to trust you all to make sure that it is done right.

We see this sad case of what happened in Haiti. My sense is that we have got some other problems that have occurred in this country, maybe not—without the headlines, maybe we don't know, but someone has got to have that Good Housekeeping Seal of Approval which you have. To me, the most basic thing is when someone is suspected of sending something in, that somebody is on top of it.

Mr. TAYLOR. Mr. Chairman, I agree with everything that you have said.

Mr. UPTON. I have to swear you in now. You should have probably stood up when we did this in the beginning. But if you would identify yourself again for the record.

Mr. TAYLOR. My name is John Taylor and I am the Acting Director of the Office of Compliance at the Center for Drug Evaluation and Research.

Mr. UPTON. If you would stand, I will swear you in.

[Witness sworn.]

Mr. UPTON. You are now sworn in as well.

Just in a minute, time is gone, but if you would give an answer and then we will continue to rotate.

TESTIMONY OF JOHN TAYLOR, ACTING DIRECTOR, OFFICE OF COMPLIANCE, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION

Mr. TAYLOR. Okay. Right now, as a part of the GMP regulations—those are the quality control and quality assurance regulations that dictate how pharmaceutical products are supposed to be manufactured to ensure their safety and efficacy—the manufacturer is supposed to determine whether or not the bulk product they are getting is from the approved supplier. So they are supposed to have in their files information regarding the bulk products that they are getting. If they run an analysis and it determines that there are impurities or that the product is subpotent, that information is supposed to be in their files; and as a part of our GMP inspections, we are looking at that and have access to this.

Mr. UPTON. I know you have access to it. The question is, if you have got the red flag that's up there, why aren't they required to tell you, so that you can take action like that, to go after them to make sure it doesn't happen again versus, oh, it is—you know, it is the third year of our inspection process, and here we are, and maybe we find it and maybe we don't, and—you know?

Mr. TAYLOR. I agree with you. That's the reason why I think it is a good idea because it gives us the opportunity on a real-time basis to have information regarding whether or not a product that is received is of poor quality; and instead of waiting between our regulatory inspections to discover that information, this gives us an opportunity to do regulatory follow-up right away, whether it be civil or criminal. So I think it is a very good idea.

Mr. UPTON. Well, why can't we get it done? This has been before you. Again, I know Mr. Dingell is not here, but it has been before you for more than a year. He is not exactly a silent individual. He usually carries a big stick.

Mr. TAYLOR. I do think we should follow up and we should follow up on it quickly. I know the idea was brought up before. I apologize for the fact that we did not run with it, but we think it is a good idea, and we are prepared to run with it and offer it. What we want to do is find the right place in the regulations where it should fit.

But that's something we think is a good idea and will help us.

Mr. UPTON. Mr. Stupak.

Mr. STUPAK. Thank you, Mr. Chairman.

Mr. Baker, if I may, if you would bear with me for a minute, I would like to ask you a question or two, and I appreciate your help in fully understanding this issue and a related issue.

First, I understand the tremendous strain that the implementation of the 1997 FDA Modernization Act has put on the resources of the FDA. However, this issue before the committee disturbs all of us here today. When I couple this issue with the other information I have been given on another potential drug safety concern, I am perplexed.

Mr. Baker, are you aware that some pharmacies are importing nonpharmaceutical-grade radioisotopes and illegally manufacturing and selling radioactive diagnostic drugs under the guise of the practice of pharmacy?

Are you aware of that going on?

Mr. BAKER. I will defer to Mr. Taylor on that. We do have information on that, yes, sir.

Mr. TAYLOR. Yes, sir.

Mr. STUPAK. How have you responded then to the concerns of the legitimate manufacturers whose FDA-approved drugs are being copied by these pharmacies, since they have brought this problem to your attention about a year ago?

Mr. TAYLOR. Well, my response would be, the Modernization Act obviously carved out some exceptions for compounding. For example, the fact that you don't have to register as a manufacturing facility, you don't have to follow GMPs; but that same exception was not carved out for radiopharmaceuticals.

Mr. STUPAK. So there is no exception for them?

Mr. TAYLOR. Right. As a result, radiopharmaceutical manufacturers still have to register with the Agency.

Mr. STUPAK. Right.

Mr. TAYLOR. And still have to follow good manufacturing practices.

Mr. STUPAK. You admitted a year ago they brought this to your attention, right? I have some letters here from June 1999, August 1999, May 12, 2000 to a Lana Ogram. Have you succeeded her in that office now?

Mr. TAYLOR. Well, she actually works for me.

Mr. STUPAK. Okay. In the Office of Compliance, right?

Mr. TAYLOR. Yes.

Mr. STUPAK. So they work for you. So if it is your policy then to ensure that patients are protected from potentially unsafe and ineffective drugs, why has no one responded in the last year to the concerns brought forth by these manufacturers?

Mr. TAYLOR. Well, sir, I have been there 6 weeks, and when I first arrived, I realized that these letters were before the office. And we are preparing responses, not only to letters that we have received from manufacturers about radiopharmaceuticals, but also letters we have received from compounders seeking clarification on our policy.

Mr. STUPAK. I realize you have been there for 6 weeks. You said this lady, Lana——

Mr. TAYLOR. Lana Ogram.

Mr. STUPAK. [continuing] Ogram works for you, right?

Mr. TAYLOR. Yes.

Mr. STUPAK. So has she followed up with these people?

Mr. TAYLOR. Well, I know that we have drafted responses that are now before our attorneys and are ready to go out. She has spoken to some of these people. We have actually done, quite frankly, some investigatory follow-up to investigate some of the allegations that are in the letter, and some of that is actually ongoing right now.

Mr. STUPAK. Okay.

Mr. TAYLOR. So we think there will be further steps in the future.

Mr. STUPAK. If you would, after this hearing sometime, and in the real near future, could you get with us? Because I would like to follow up more on this detail.

Mr. TAYLOR. Sure.

Mr. STUPAK. If you are doing something, we want to know what it is, so we can get back to these folks. I want to follow up that part of it. I am really interested in this very serious allegation here.

They use the radioisotopes, I am sure you know, for very serious illnesses and diseases and for detection, and I just want to make sure we are doing all we can so those who are faced with a serious injury are getting the best possible coverage.

Mr. TAYLOR. Sure.

Mr. STUPAK. Mr. Baker, if I can jump back to you then, in June 2 correspondence to this committee, you reported that—and I am quoting—"The number of foreign drug manufacturers that have shipped to the U.S. but have never been inspected by the FDA is approximately 4,600." You go on to say, in a quote again, "The number of such firms located in China is 623 and the number located in India is 409."

Mr. Baker, isn't there evidence that both China and India have had significant problems with drug counterfeiting in the past?

Mr. BAKER. Yes.

Mr. STUPAK. Okay. What can you tell us about the 623 firms located in China that are apparently shipping or have shipped to the U.S., but have never been inspected?

Mr. BAKER. Right now, we are going through the entire 4,600 list. That's one of the things that I instructed the staff to do. I wanted answers, and I wanted answers right away. We should have some basic information on anyone that is shipping into the country.

One of the things we are dealing with here is, a lot of these APIs may have been entered and then they would be in the system as entered from an API source, but it goes to a nonpharmaceutical source. So we are looking at the issues associated with those entries right now.

Mr. STUPAK. Okay. Do you know if any of the 623 Chinese firms mentioned above are tier 2 or tier 3 firms? Do you know?

Mr. BAKER. Yes, they may be, certainly.

Mr. STUPAK. Okay. Do we know if they meet all the current good manufacturing practices?

Mr. BAKER. No, we don't.

Mr. STUPAK. We don't know that. Okay.

So we should be concerned then, without that knowledge, about products some of these companies are shipping here to the U.S. then, right?

Mr. BAKER. Yes, sir.

Mr. STUPAK. Okay. What about the Indian firms, the 409, are they tier 2, tier 3?

Mr. BAKER. Yes, sir, I am sure they are.

Mr. STUPAK. Again, we don't know if they are—the current good manufacturing practices, we don't know if they follow that standard?

Mr. BAKER. That's correct, sir.

Mr. STUPAK. Okay.

You indicated in your statement that you appreciate the support of Congress, and then trying to do your investigation, and I mentioned in my opening statement that—what are the resources you need? If we are not providing you sufficient resources, what exactly do you need to really get at this issue?

I am hearing here this morning already that letters are about a year old; they are not being answered; attorneys are looking at them; we don't know if these Chinese or Indian firms are following. What do you need specifically to really enforce this, to correct some of these problems?

Mr. BAKER. A combination of things. Obviously, part of the solution would be the FTEs to do a better job of inspecting. It is also having that comprehensive and linked computer system to adequately assess data to make sure that we are able to quantify information that's coming in. We are trying to pull it now from several independent data bases. It is not an efficient system.

Then, obviously, we need a targeted approach to criminal investigations, both through our Forensic Chemistry Center and our Office of Criminal Investigations.

Mr. STUPAK. Can I ask you one more—if I may, Mr. Chairman?

Do you know now if any of this material is being sold through some of the Internet Web sites to U.S. citizens that's already counterfeited drugs or are substandard drugs?

Mr. BAKER. I am not aware of that, no, sir.

Mr. STUPAK. Okay.

Have you done a review of it, a screening?

Mr. BAKER. We have done some purchasing of products offered on the Internet, and we have done some analytical work associated with those products. Thus far, the products have proven to be mostly from domestic suppliers. But then, given the scope of the Internet, the number of places potentially offered and our ability to analyze, I wouldn't rule out that being a problem; just simply, we haven't uncovered it at this point.

Mr. STUPAK. You said they were from U.S. products, but when we had our hearing on the Internet sales, most of the Web sites are from other countries. Very few are from the U.S. So have you checked any of the Web sites that are located——

Mr. BAKER. We have been checking Web sites, yes, sir.

Mr. STUPAK. Because most of those are not U.S. products; they are other countries.

Thank you, Mr. Chairman.

Mr. UPTON. Mr. Burr.

Mr. BURR. Mr. Baker, does the FDA believe that Americans have died or been injured because of counterfeit or unapproved bulk ingredients?

Mr. BAKER. We have information that there were certainly injuries associated with counterfeit products, yes, sir.

Mr. BURR. Is that answer yes?

Mr. BAKER. Yes, sir.

Mr. BURR. Mr. Taylor, you work in what capacity at the FDA?

Mr. TAYLOR. I am the Acting Director of the Office of Compliance.

Mr. BURR. Would the Office of Compliance come under the Office of Regulatory Affairs?

Mr. TAYLOR. No. I report to the Director of the Center that approves drugs; I report to Dr. Woodcock. We are peers. We are a sister organization of Mr. Baker.

Mr. BURR. Okay.

Mr. Baker, I understand that on Monday you met with the committee staff.

Mr. BAKER. That's right.

Mr. BURR. At that meeting, the staff presented you with a confidential report on counterfeit and fraudulent practices in the bulk drug industry. You said, if I understood them correctly, you had never seen that document; is that correct?

Mr. BAKER. Yes, sir.

Mr. BURR. Well, my understanding is that the Office of Criminal Investigation, which reports to you, had a copy of this report, but didn't share it with you, even in your preparation for this hearing. Is that correct?

Mr. BAKER. I did have it in preparing for this particular hearing today.

Mr. BURR. Why wasn't it shared with you if they report to you and you are in charge of this?

Mr. BAKER. The information was shared with me. I didn't recognize the document as it was presented to me. The basic information was shared with me in February 2000. At that point, I allocated funds to do some targeted inspections and analytical work associated with APIs and importers.

Mr. BURR. Is there a communications problem at the FDA?

Mr. BAKER. No, sir, I don't believe so. I think we have got good communications across the various programs.

Mr. BURR. Let me ask you about a memorandum that we entered into the record. It was a memorandum from Carl Nielsen. I believe he is the Director of Import Operations. I believe you appointed him. Is that correct?

Mr. BAKER. Yes, sir, that's correct.

Mr. BURR. It was a memo from him to Frank Forgon?

Mr. BAKER. Forgione.

Mr. BURR. Forgione. Excuse me.

This is on counterfeit imported human Rx bulk drugs. In this memo, Mr. Nielsen states, "It appears there have been deaths associated with the use of generic prescription drugs made from counterfeit bulk drugs supplied by Flavine."

Is that the documentation that you were referring to when you said the FDA believed that, in fact, Americans had died?

Mr. BAKER. That actually was referring to that documentation and then to adverse events that have been associated with some of them.

Mr. BURR. So is there more than this memo that would suggest that there is a health problem?

Mr. BAKER. I don't know that I can answer that without looking at a number of documents to see what we have.

Mr. BURR. Well, I would hope that your staff, in preparation for this hearing, would have at least shared with you the documents that existed that might deal with deaths that had occurred from contamination or counterfeiting of drugs.

You believe that that is taking place?

Mr. BAKER. Well, we have certainly investigated a number of deaths and injuries associated with counterfeit drugs and allegations of counterfeit drugs, yes, sir.

Mr. BURR. He also observed in this memo—let me read it, and I quote—”There is, in effect, little or no FDA control of bulk drugs coming into this country, and there is currently no ongoing enforcement action to serve as a meaningful deterrence to the trafficking and use of counterfeit or unapproved bulk drugs.”

Have you read that statement?

Mr. BAKER. Yes, sir.

Mr. BURR. Is that the case?

Mr. BAKER. At this time, we do not have a specific enforcement action going on. We do have investigations open.

Mr. BURR. Can you share with me what the date of this memorandum was?

Mr. BAKER. August 1996, I believe.

Mr. BURR. May 15. Of what year?

Mr. BAKER. I am sorry, 1996.

Mr. BURR. Okay. It has been 4 years since this revelation was made at the FDA. How long should we wait?

Mr. BAKER. I don’t think we should wait. We have to be proactive, and that’s what we are attempting to do now is, be proactive and identify——

Mr. BURR. How long have you been in your capacity?

Mr. BAKER. About a year.

Mr. BURR. About a year?

Mr. BAKER. Yes, sir.

Mr. BURR. So I can’t date back to 1996 and ask you from 1996 to a year ago why something didn’t happen. That is unfair. But clearly the FDA, in their own memoranda, knew in 1996, May 15, that they had a problem; they had a problem and they had deaths.

What has happened since you have been there that assures this committee that this is not continuing?

Mr. BAKER. Our ongoing efforts to improve the overall processes.

Mr. BURR. What are those efforts? What are those improvements?

Mr. BAKER. Well, some of them we just covered in my testimony.

Mr. BURR. Those are in response, I believe, to the fact that Congress now has this on their front burner, that John Dingell and Bart Stupak and Ron Klink and Fred Upton and Tom Bliley are concerned with this and we have come up with a series of things that we are going to run to the Hill and present. This is 1996, Mr. Baker.

Mr. BAKER. Yes, sir.

Mr. BURR. What initiatives happened before Congress got interested in the deaths of Americans and the counterfeit of drugs and the contamination of bulk drugs coming into the country?

Mr. BAKER. Well, one of the initiatives that occurred before I knew this was going on was in February of 2000 when I directed the funding of the initiative out of our Forensic Chemistry Center to do specific, targeted inspections and sampling and analytical work at specific import sites.

Mr. BURR. I hope you understand my frustration.

Mr. BAKER. Yes, sir, I surely do.

Mr. BURR. And this is today’s news article, and the chairman has already referred to it, when your quote is, “Surprise is probably an understatement," surprise that there are so many entities out there that are uninspected.

Gosh, 4 years ago; a year ago you came in, we are still in the mode where we are surprised? I am hopeful that through this hearing you will understand the urgency of a solution to this problem.

Mr. BAKER. Yes, sir.

Mr. BURR. Mr. Chairman, I yield back.

Mr. UPTON. Mr. Strickland.

Mr. STRICKLAND. Thank you, Mr. Chairman.

Mr. Baker, much of the inability to detail precisely who these foreign firms are, when they were last inspected, whether they are manufacturing in accordance with current good manufacturing practices and so on, is because of an information technology problem.

The FDA has a multitude of data bases that don't properly interact with each other; is that correct?

Mr. BAKER. Yes, sir, that is correct.

Mr. STRICKLAND. Isn't that mainly the problem with the OASIS system, or are there other systems who are at fault here?

Mr. BAKER. There are several systems that interact, that we use information from, in order to make assessment of products. In addition to the OASIS system, which is the entry system for FDA, where we actually have items come in on a screen and our people look at the items for approval of entry into the United States, we have a FACTS data base which is our data base which covers foreign establishments and domestic establishment inventory. That latest upgrade came on-line last September. We are developing the data base there.

The OASIS system feeds information into the FACTS system; as an example, whenever a firm offers a new product for entry into the United States, it automatically updates FACTS with the information that this is a new manufacturer, and it creates an FEI, Federal Establishment Number, there.

Mr. STRICKLAND. Okay. The FDA obviously has had problems for years with these foreign inspection data bases. You have apparently been telling this subcommittee—I am fairly new to this subcommittee, but I think you have been telling this subcommittee for years that the problem is soon to be fixed. So I guess a fair question to ask you would be, when is it going to be fixed?

Mr. BAKER. We are making efforts at this time to go to a Windows-based environment. I have been advised that that will be in place by the end of 2001. That way we will be able to work better across the data bases structurally.

In addition to that, I have asked—I beg your pardon?

Mr. STRICKLAND. I am sitting here thinking, when you said the end of 2001, I am thinking we could plan, execute, carry out, conclude a war in that length of time. It just seems like an unreasonable period of time. Is it impossible for you to accomplish this sooner than the end of 2001?

Mr. BAKER. Well, our Chief Information Officer basically drives the structure of the information systems within FDA. I don't have a good answer for you why it would take that length of time.

Mr. STRICKLAND. I would like to yield to my colleague.

Mr. STUPAK. On this IT problem——

Mr. BAKER. Yes, sir.

Mr. STUPAK. On this IT problem, can you get back to this committee within a month and tell us formally what you are going to do and how it is going to be fixed and what needs to be done to fix it?

Mr. BAKER. Yes, sir.

Mr. STUPAK. This has been going on for some time. I certainly agree with my colleague here that the end of 2001 just doesn't seem right.

I would think that within 30 days you could come back to this committee, under the chairmanship of Mr. Upton, and tell us exactly what you are going to do, what has to be done, how we do it—and hopefully it is not going to be 2001—in writing.

Mr. BAKER. Very definitely, yes.

Mr. STUPAK. Thanks for yielding.

Mr. STRICKLAND. Yes. And if you can't do it, you need to come back and tell us you can't do it and why you can't do it. That seems to be a fair request on our part.

Mr. BAKER. Yes, sir.

Mr. STRICKLAND. Mr. Baker, does the FDA have a timetable—well, the 2001, that's your current timetable, the end of 2001?

Mr. BAKER. That's for the overall architecture of the system to be completed and carried out across the Agency, on the wide area network.

Mr. STRICKLAND. That's the architecture. That doesn't mean——

Mr. BAKER. Individually, it doesn't——

Mr. STRICKLAND. I assume architectural plans, but does that mean that there would be—even under your current plans, that this would be accomplished by the end of 2001?

Mr. BAKER. I have been advised that it is due to be accomplished by the end of 2001. That doesn't mean we can't do some things with our current systems, which is what I am proposing here today, and the information I gave you in some of my oral testimony of things we are going to do—we are going to do immediately.

Mr. STRICKLAND. Mr. Baker, what percentage of the bulk raw material used to manufacture these drugs globally would you consider to be counterfeit?

Mr. BAKER. I don't know that I can quantify that, the amount that may be counterfeit, of a global nature. I have seen reports from WHO and others that indicate it could be quite high, 50 to 70 percent.

Mr. STRICKLAND. Fifty to 70 percent? And then there may be other of these drugs that are substandard, or in other ways adulterated; is that correct?

Mr. BAKER. Yes, sir.

Mr. STRICKLAND. Which countries are the most problematic when it comes to selling these substandard counterfeit bulk ingredients?

Mr. BAKER. There are quite a few countries that have been discussed. Specifically, we have had problems with China and India, in fact.

Mr. STRICKLAND. So you would say China and India would be near the top of the list if you were making a judgment on that?

Mr. BAKER. Certainly they would be on the list, yes, sir.

Mr. STRICKLAND. What countries are the most problematic, in your judgment, when it comes to selling substandard or counterfeit finished products, not the bulk materials, but the finished products?

Mr. BAKER. I don't know that I would have a good answer for you there because the capability in any number of countries is such that they can market counterfeit drugs. It is an ongoing problem. We even see it from Mexico.

Mr. STRICKLAND. One final question, Mr. Baker, and perhaps this has already been asked; I am not sure.

But in your judgment, should the FDA require that all U.S. firms that import raw pharmaceutical ingredients certify in writing that each of their sources meets current good manufacturing practice requirements; and, if not, why not?

Mr. BAKER. Right now, we do require that they provide a certificate of analysis or they have ongoing records, laboratory records, to indicate that the product meets the standards for manufacturing in accordance with the approval of their product.

Mr. STRICKLAND. But you have told us that you can't know for sure if these firms meet current good manufacturing practice requirements. Apparently, that is a particular standard that is a recognized standard.

Would it not make sense to require these firms to provide you with assurance in writing that the materials they are using have been manufactured under these conditions?

Mr. BAKER. That may be helpful. I will defer to Mr. Taylor here, but I will say that they are required to, by laboratory analysis, demonstrate that the products are meeting a standard of purity there.

Mr. STRICKLAND. But not necessarily meeting the standard of current good manufacturing practices? Is that right?

Mr. TAYLOR. Well, I just want to expand on his answer.

For prescription drugs, as a part of the approval process, when an approval packet is submitted to the Agency, one of the pieces of information that also must be submitted is the name of the supplier of the bulk product, essentially the active pharmaceutical ingredient. When that information is provided to the Agency, the Agency is then required to go to that facility and inspect to determine whether or not they are in compliance with good manufacturing practices. If they are not, then not only does the approval not move forward, they are not allowed to import that product into the United States. That's for prescription drugs.

Now, obviously we have talked today about the fact that there are some facilities that we don't know about and we have to do a better job with that; and some of those facilities might be supplying materials for over-the-counter products, which would not fall within this preapproval rubric.

But my point is that they are supposed to be in compliance with GMPs. They are supposed to provide that information to the Agency about the compliance with GMPs so that we can go out and make sure that their statements are correct.

Mr. STRICKLAND. Thank you, Mr. Chairman.

Mr. UPTON. Mr. Bryant.

Mr. BRYANT. Thank you, Mr. Chairman. And we are going to have to be subject to leave here and vote, and I want to be very brief in my questioning.

Understanding that you have only been in your position a year, I mentioned in my opening statement my concern about not—since 1996, not coordinating with Customs. And perhaps you could, if you don't know the answer as to why that's not ongoing, you could later file a letter as an exhibit to your testimony with an explanation as to why that's not being done; and hopefully, maybe, some indication that your office might reconsider that. Is that fair?

Mr. BAKER. Yes, sir.

Mr. BRYANT. Now, in your position, are you the person that has the authority to control the agents out in the field, the ones at the places of entry in this country and wherever else you have investigators trying to work on this problem of counterfeit bulk drug imports?

Mr. BAKER. Yes, sir.

Mr. BRYANT. You are the person responsible?

Mr. BAKER. Yes, sir, the field operations report to me.

Mr. BRYANT. Now, where does Mr. Taylor fit into this with you? If you could be brief.

Mr. TAYLOR. Sure.

I head the Office of Compliance within the Center for Drugs. The Center for Drugs is a sister agency within FDA, and we help ORA determine whether or not a specific manufacturer or a specific product is in compliance with Federal law.

Mr. BRYANT. Okay.

Now, Mr. Baker, is your job 100 percent dedicated to this particular problem, or do you have other responsibilities in the area of regulation?

Mr. BAKER. We regulate all foods, drugs, medical devices and cosmetics, and the attendant problems associated with those. So we cover the spectrum.

Mr. BRYANT. Do you have somebody in your office whose job it is to be 100 percent dedicated to this particular problem of importing counterfeit bulk drugs?

Mr. BAKER. No, sir.

Mr. BRYANT. Where I am going with this is trying to find within the scheme, the chain of command, who can come in here and we can complain to. We have got a lot of responsibilities and we cover the land up here. We expect people like you, or whoever in your office is in charge of this problem, dedicating 100 percent of their time and assets to that to do a better job in this situation; and it is not happening.

So every year or two we have to drag you folks in and gripe and moan at you; and then nothing seems to happen, particularly in this case, since we are going back to 1996.

I am just wondering, if that was my job, 100 percent of the time, to make sure that we have enough agents out there at the ports and doing these inspections and operating the computers so that the data bases can come together and maybe working with other agencies like the Customs to do this, that's who I want to know.

Whose job is it to do that? Because obviously they are not doing a good job. And if we could get those people motivated, maybe we wouldn't have to do this, you know, devote our time to this oversight.

Mr. BAKER. We do have a Director of Import Operations. That's Mr. Carl Nielsen, as they mentioned earlier, and that covers our import activities. Our foreign inspections are covered another component within ORA. There is ongoing communication between those.

Mr. BRYANT. I would like to know if Mr. Nielsen is concerned with the fact that of the 310 points of entry we have only got 68 full-time equivalents in the field. And I am sure that—at the 68 that are covered, I am sure we have several at one location, so probably more than——

Mr. BAKER. Actually, sir, that's the way they set it out, based on funding. We have about 254 people in the field reviewing all FDA-regulated products. About a quarter of their time is spent reviewing drug imports, and so that's where the 68 came out as an FTE figure. We actually have about 254 people in the field.

Mr. BRYANT. I am going to read you a couple of quick questions because my time is running out, and we have got a vote. You can again late-file your answer to these.

Would you favor assigning agents from the Office of Criminal Investigations or other FDA personnel to post in Asia and Europe for the primary purpose of gathering information in support of this counterfeit drug initiative?

Second, has the FDA considered a joint FDA industry effort to develop a program to eliminate counterfeit bulk drugs?

Third, would you favor developing new systems within the FDA to identify counterfeit drugs and other unapproved or illegal drugs that enter the country?

Fourthly, does the FDA favor exploring new technologies to help ensure the safety and security of our drug supply, such as tagants and drugs on containers or labels.

And finally, this is important, what in your opinion can this committee or Congress do to approve your ability, the FDA's ability, to further assess the problem and investigate, interdict and control counterfeit drugs?

If you could maybe get a copy of this testimony and answer those specific questions, as well as this issue of the Customs, I would appreciate it very much.

Mr. BAKER. Yes, sir.

Mr. UPTON. I would just note that we do have about 5 minutes left in the vote, so we will temporarily adjourn here and we will come back at 12:45.

[Brief recess.]

Mr. UPTON. Welcome back. We are not expecting a vote for a couple of hours, but I don't expect this subcommittee hearing to go on for a couple hours more either. So I think we will be okay in terms of the timing.

I know a couple of members are on both sides of the lanes here, and again we have other subcommittees within our committee meeting, and many of us are on multiple committees. And we have an important piece of legislation on the floor; I know that I have an amendment that will be up a little bit later this evening as well.

Mr. Baker, I don't know if you saw this article a couple of weeks ago, it was in Dickinson's FDA Webview. There is an article entitled "Counterfeit Bulk Drugs Not a Health Issue for United States, FDA Says."

The article went on to say that "Counterfeit bulk drugs entering the U.S. are not a public health problem for this country, FDA Center for Drug Evaluation and Research Director Janet Woodcock told FDA Webview yesterday." The article went on to further say that Woodcock said that "Counterfeit APIs have a low priority at FDA because U.S. manufacturers have not expressed heightened concern about them and finished dosage form makers are the ones responsible for assuring the integrity of drugs sold in the United States." All of that being in quotes.

What is your reaction to the statements attributed to Ms. Woodcock? Are they accurate?

Mr. BAKER. Well, Mr. Chairman, I would have to say, obviously we believe there is a counterfeit problem, both in this world and potentially within this country. We have had problems quantifying that, obviously.

What I think Dr. Woodcock was speaking to was simply the controls within the domestic supply whereby the manufacturers are doing heightened testing and certificates of analysis associated with the products. So I don't believe she was saying that coming into the country, that this may not be a problem. I think she was saying—addressing the domestic supply.

Mr. UPTON. Now, you all, as I understand, agreed to spend some money to investigate this; is that right?

Mr. BAKER. Yes, sir.

Mr. UPTON. How much money was that that you——

Mr. BAKER. The recent one was $59,000 for purchasing of products for analytical work.

Mr. UPTON. Tell me exactly what the money was to be used for. I mean, what was the money supposed to do?

Mr. BAKER. We are going to be targeting specific importers, particularly those that have a heightened profile for importing and distributing counterfeit product, plus targeting and sampling for analysis and analyzing product that would fit the profile of a potentially counterfeited drug.

Mr. UPTON. Are you going to look at India and China as part of that?

Mr. BAKER. Yes, sir. Their products would be some of those that would be looked at, yes, sir.

Mr. UPTON. All right. When you begin to look into those two, and I think it was Mr. Stupak who raised the large number of firms over there that, in fact, there are no inspections.

Are you having trouble with the governments of those two countries? What is the access to those facilities like?

Mr. BAKER. We have been provided access to the facilities that we have asked to inspect. We do go through the process of notifying the foreign government, establishing the travel, and then conducting the inspections.

Mr. UPTON. Have you ever been denied access? Is there a case where you have been denied access to look at some of those firms?

Mr. BAKER. I am not certain. I would have to check. I am not aware of it, though.

It is no. I am told it is no.

Mr. UPTON. It has never happened. According to the June 1998 gold sheet, William Grosse, quality assurance director at Eli Lilly, spoke about the growing threat of counterfeit bulks at the meeting of the Drug Information Association. He said, "sooner or later, we are going to have a catastrophe" in the United States. He mentioned that the sale of counterfeit products worldwide is increasing at a rapid rate. He cited figures suggesting that 40 to 60 percent of drug products sold in Malaysia and Indonesia, 25 sold in Mexico and 78 percent sold in the United States are counterfeit.

He went on to say that manufacturers are collecting a lot of information on the problem but do not have a very good place to take it.

That sort of goes back to my initial question at the beginning.

In light of that article, is Dr. Woodcock's assertion that U.S. manufacturers have not expressed a heightened concern an accurate one?

Mr. BAKER. They have expressed the concerns to us about the overall counterfeit situation. We do have ongoing dialog with their security chiefs, and we have routine meetings to discuss issues associated with counterfeiting and other problems in the drug industry.

Mr. UPTON. Has there been an outcry by the pharmaceutical industry that they would like to have you all regulate or get an announcement, some notification, information, when, in fact, they suspect that they have received tainted compounds?

Mr. TAYLOR. Not that I know of, Mr. Chairman.

Mr. UPTON. You know, we thought on this panel that it is a wise idea. I am just wondering if they have voiced such support independently as well.

Mr. TAYLOR. No, sir, and even though I think it is a good idea, I am not sure how that good idea will be received. When we put the idea out, we are going to have to do so as a part of rulemaking, and that will give industry and others an opportunity to comment. But I have not heard anything as of this date as to whether or not industry likes that idea.

Mr. UPTON. Okay.

Mr. Strickland.

Mr. STRICKLAND. Thank you, sir.

Mr. Baker, how often is the FDA supposed to be inspecting foreign firms that export drugs or drug products to the U.S. for GMP practices?

Mr. BAKER. Well, it would be great if we could impose the same standard on them that we do on our own domestic suppliers. The reality of our inspections, is that they are driven by the application process, that is, to get a drug approved, and then we go to the tiered process after that as a follow-up surveillance, or going in for cause.

Mr. STRICKLAND. What is the practice for our own domestic firms?

Mr. BAKER. We try to get in there at least every 2 years, more often for cause.

Mr. STRICKLAND. Two years?

Mr. BAKER. Yes, sir.

Mr. STRICKLAND. Now, it has been confirmed with your staff that there are several incidents where firms, these foreign firms that export to us, haven't been inspected by an FDA official in at least 7 years. Why is that?

Mr. BAKER. Quite honestly, sir, a good bit of it has to do with the resources available to do the overseas inspections.

Mr. STRICKLAND. Do you think 7 years is too long?

Mr. BAKER. Yes, sir.

Mr. STRICKLAND. What if a foreign firm makes significant changes in their practices during this extended intervening period of time between inspections; how would the FDA know such changes have occurred if it doesn't inspect more frequently? It wouldn't, would it?

Mr. BAKER. No, we may not. They are obligated to tell us about any changes in the processes, and hopefully, if it is an API firm, the final dosage manufacturer will be notified and they will know about any changes.

Mr. STRICKLAND. What are the implications of these infrequent inspections on public health?

Mr. BAKER. Well, again, that's hard to quantify, but it certainly would be an at-risk situation.

Mr. STRICKLAND. So we can reasonably conclude that because these inspections are not occurring, that American citizens who purchase products which may be made from these imported goods are at risk; is that a reasonable conclusion?

Mr. TAYLOR. I am not sure we can draw that conclusion.

Mr. STRICKLAND. Do you conclude that they are not at risk?

Mr. TAYLOR. No, I cannot conclude that, either. I think that by not having regular inspections at a shorter interval, obviously it does not serve the same deterrent effect as if we were in there over and over again, but I am not sure I could draw the conclusion that negatively——

Mr. STRICKLAND. Well, if there aren't health and safety implications to the inspection process, why have an inspection process? And if the inspection process is not occurring in a timely manner, it seems very reasonable to be able to say here today that American citizens are being placed at risk due to a lack of inspection. Is that—I am not trying to be unreasonable.

Mr. TAYLOR. Right.

Mr. STRICKLAND. But I don't want us to be fuzzy about our conclusions when we don't have to be.

Mr. BAKER. The potential is there, yes, sir.

Mr. TAYLOR. That's right, and that's why we have those regulations in place in the first place.

Mr. STRICKLAND. The FDA has clearly defined its resource limitations in the area of conducting these GMD inspections on foreign firms. What are the limitations, in your judgment, and specifically, and if you could be as candid as possible, what do you need in order to do an adequate job, what resources? If you can name an estimated amount of money or a number of inspectors, what is it specifically that you need that would enable you to come before us a year from now, and we would all be very pleased with what had happened in the intervening 12 months?

Mr. BAKER. Fine. Right now we have 175 FTEs that are available to do foreign drug inspections, that are drug inspectors available for foreign drug inspections. I would like to add that they also have domestic responsibilities, so they have to cover the domestic side as well. We are pulling personnel out of the domestic side any time we do these foreign inspections. That's one issue.

Having the IT available, which we have discussed earlier, where we can get meaningful data and have it real-time available to our inspectors is another issue. When I came on board here a year ago, we didn't even have all of our investigators equipped with laptop computers, which they are now.

Mr. STRICKLAND. Mr. Baker, I don't see why you just don't, if necessary, contract with some firm that has the expertise necessary to do this, bring them in and in perhaps 2 months, that seems like a reasonable period of time, have this IT problem solved. It just seems that this is a problem that doesn't need to drag on and on and on.

Mr. BAKER. Absolutely. I totally agree.

Mr. STRICKLAND. I want to ask you, sir, if you would provide to us, and Mr. Chairman, I would like your support on this request, if I could have it. It seems reasonable that we would ask for a formal plan within 2 months as to how you plan to accomplish this, and in that plan, you lay out your problems and lay out your lack of resources, if there is a lack of resources. That seems like a reasonable request from us, and I would like for you to agree today to do that.

Mr. BAKER. We will do that, yes, sir.

Mr. STRICKLAND. One final question, Mr. Chairman.

I am intrigued by the problems with China and India, especially that have been noted here. Do you know that if China was a part of the World Trade Organization, that our ability to prohibit them from sending in these materials into our country would be inhibited—that our enforcement ability would be inhibited because of their membership in the World Trade Organization, if we could keep that from happening simply because their firms did not meet FDA inspection or approval or standard? Could you answer that for me.

Mr. BAKER. I don't know if I can. I don't know what the impact is of them entering the WTO and the problems associated with GMPs. I don't know. I am not a trade lawyer.

Mr. TAYLOR. I don't know the answer, either, but we certainly can get back to you with an answer.

Mr. BAKER. Yes, certainly.

Mr. STRICKLAND. If you would, I would find that very helpful, and one further question. Why don't we just decide that if a country is engaging in these practices, or foreign firms in these countries are engaging in these practices and they are identified, that we just simply say we are not going to allow business with you in the future?

Mr. BAKER. Well, there are Customs laws and there are also, of course, the FDA laws that drive appeal rights and everything else associated with entering products into the country, and importers, like anyone else, would have their day in court. So it would be a difficult situation to stop it out of hand. I don't know that anybody has the authority just to make that declaration.

Mr. STRICKLAND. Well, I fear that China's involvement in the WTO may make the ability to regulate and enforce even more difficult. So if you would get back with me on that issue, I would appreciate it.

Mr. TAYLOR. Certainly.

Mr. BAKER. Sure.

Mr. STRICKLAND. Thank you, Mr. Chairman.

Mr. UPTON. Thank you.

Mr. Baker, in the letter that was sent to Chairman Bliley May 31, the FDA says, at this time there are neither specific allegations concerning bulk counterfeit drugs nor any concern of a systematic problem.

I want to just refer again to some of these letters, which I think you have a copy of. Maybe you can turn them around. You will see the same, just so that Mr. Baker can see them.

This is a fairly clear case, I think you can see, of a firm trying to repackage, actually the other letter you will see it has the same signature, but they are actually trying to show the original source of these compounds to be from West Germany, which, of course, would have been prior to 1990—instead of coming in from China.

In light of the poor inspection in China, and this being a problem, I just find it difficult to believe that you weren't aware of any systematic problem, and that this should not have been—or this should have been referred to the IG or to somebody who actually could have begun to look into this. I mean, we are frustrated on this panel, Republicans and Democrats alike, with trying to make sure that, in fact, there is a safety net out there. You all have that responsibility. Yet, there are literally thousands of companies that we don't know about. We saw the well-publicized deaths, the 89 deaths in Haiti; your admission that, in fact, we have had problems in this country, and just some basic investigatory tools that ought to be utilized, it just seems, haven't been done. That's our frustration up here. I know I speak for Republicans as well as Democrats when I say that.

We want to make sure that you have the tools, that you have the FTEs, full-time equivalents, the people that are in power. We want the pharmaceutical companies to be able to tell you with 100 percent certainty whether, in fact, the material they are getting is safe or not, and not only the big players, the Eli Lillys, the Mercks, the Pharmacias, the Upjohns, but the generics, too. They make billions of pills for a variety of different medicines—whether it be aspirin or a number of other things, particularly when the patents expire.

It seems as though there has been ample evidence, whether it is the materials here or others, that, in fact, the FDA should have acted on, should have promulgated some regulations, should have been able to get some feedback, particularly in light of the fact that you admit that there are problems that are out there. That's what frustrates us.

Mr. BAKER. Well, we have taken the situation seriously. We have initially trained, we have completely trained 30 FTEs, specifically in the area of counterfeiting, and we are taking that training out beyond that 30. In addition, in July, we are going to be doing Customs training with our staff, and the Customs Service is going to be instructing on their laws. We are going to do some strategic problem-solving and a number of other things so that our people are better able to work jointly with Customs and can use authorities vested in Customs law to get at some of these various counterfeit issues here.

So we are taking it very seriously. I can tell you we also have some frustration and we will move forward with these things.

Mr. UPTON. Now we have more port of entries for these products than we have inspectors looking out for it, is that right?

Mr. BAKER. Yes, sir, that is true. In the instance of APIs, though, we have about 90 percent of them going into roughly 8 to 10 ports. So we are able to concentrate some resources to deal with APIs in certain areas, but it doesn't solve the overall situation, and as you are aware, we do get APIs in all of those ports, although maybe not in large numbers.

Mr. UPTON. As I understand it, as these products come in from overseas, they are not necessarily saying they are going to Merck or Pharmacia or Upjohn. It is going to ABC warehouse, you know ABC trucking firm—I mean, it is going to some, I almost want to say "generic," I won't, but perhaps some nonpharmaceutical name and once it is there, it is gone, right? I mean, you can't really track it, is that right?

Mr. BAKER. It makes it most difficult, yes, Mr. Chairman. In fact, we are dialoguing right now to see what our regulatory authority is to require the identification of the ultimate consignee. That is something we are looking at to see if we do have the regulatory authority to do it.

Mr. UPTON. Could you let us know? When do you expect to come up with a conclusion to that question?

Mr. BAKER. I hope to have it within the next 3 or 4 weeks.

Mr. UPTON. I think we would like to know what that answer will be.

Mr. BAKER. We will be happy to inform you, yes.

Mr. UPTON. Where can we be helpful? What roadblocks do you see? I mean, are there some other things that have been identified that we have not touched on today?

Mr. BAKER. No, we have done a pretty good job of touching on things today.

Mr. UPTON. Yes. This was something I was going to ask. What about the ability to get criminal records from law enforcement agencies from across the land, across the ocean, from foreign law enforcement authorities on Custom brokers?

Do you have that authority?

Mr. BAKER. We have had good working relationships with a number of the foreign entities and have been able to get records, but obviously you can't always get records, depending on the country.

Mr. TAYLOR. Yes. I believe our experience is varied, depending on what country we are dealing with. So there have been instances where it has been difficult to get that information in the past.

Mr. UPTON. What countries have been particularly difficult?

Mr. TAYLOR. Well, at one point in time, and this has improved dramatically, so this isn't the case today, when we were investigating Flavine several years back, we had problems with the German authorities sharing information with us. But our relationship with them is strong today, and that's no longer the case, and we used that case as a good stepping stone to building a better relationship.

Mr. UPTON. Going back to the problem with the Haitians' deaths, what was the FDA's reaction to those 89 deaths? Was there any tracking here in terms of those same substance coming from China that may have tainted our supply at all? Was there any red flag that went up right away?

Mr. TAYLOR. Sir, I apologize. I don't know. I wasn't intimately involved.

Mr. UPTON. You weren't there.

Mr. BAKER. I was in the State of Texas. I can tell you that there was quite a bit of investigative activity at the Federal and State levels when that occurred, to ensure that we didn't have product in our markets, but I was not at the FDA at that time.

Mr. TAYLOR. I was just informed that we did put an import alert in place and we followed up on the shipments. The import alert was put in place so that the product could not continue to come in from China, and there was other follow-up to trace the shipments of the product itself at that time.

Mr. UPTON. Was any found?

Mr. TAYLOR. Apparently, the answer is yes.

Mr. UPTON. I knew the answer. And what happened?

Mr. TAYLOR. It was destroyed, apparently.

Mr. UPTON. So it could have happened here?

Mr. BAKER. Yes.

Mr. TAYLOR. It is possible, yes.

Mr. UPTON. Do you know—and I don't know the answer to this. Do you know how much was found? How many shipments? What the size of the product was? And where was it found? Where in the pipeline was it?

Mr. BAKER. One in California and on the East Coast. There were two shipments that we found that were basically in the pipeline at the time.

Mr. UPTON. I mean, I just can't imagine a greater nightmare for a family, you know, to find out that something that they might buy over-the-counter or prescribed by their physician, usually an individual of great trust, just to find out that it was tainted, and, you know, may cause some serious illness or even death. That's why this subcommittee feels very strongly that we want protection, and it has got to be perfect. When we are able to identify, whether it be documents like this or stories of what has happened in other countries and by chance, thank God, find them before they impact Americans, that you have the tools to protect us all.

Again, it goes back to the pharmaceutical companies don't want to have a tainted product out there. No way. I would like to think that the Agency would, in fact, deliver on what is a request by a number of us here to make sure that that communication channel is wide open, and that when there are serious threats or uncovering of evidence to suggest that a certain firm or a certain plant anyplace in the world is delivering a product that's less than adequate, that you have the tools to go right away to make sure that it is stopped, that there are consequences for that firm as well as perhaps individuals, and that we have an Iron Curtain of preventing that stuff from getting into the mainstream.

That's your role and from up here on this dais we want to make sure that you have the tools to do that. So I would suggest your message back to the people that work for you and the people that you work for is that that message be heard loud and clear when you get back to your office this afternoon. This is something that I think we want to continue to follow up on, and whether it be July or September, to have another hearing to find out exactly what is going on. And that we do a job as well listening to some of the pharmaceutical firms and others to find out how we can better help you make sure what happened in Haiti, and has happened in the United States—maybe we have discovered it, maybe we haven't—the system is in place so that we don't have any questions.

I guess one last question here. We have got an e-mail that was dated November 1997 from then-Deputy Commissioner Mary Pendergast concerning an international drug trader called Helm. I don't know if you are familiar with that. Do we have that that we can share with them? I don't know if you are familiar with this offhand.

She writes, and I quote here, that "Helm Voss are notorious in other parts of the world for not telling the truth about what they are shipping.

"Apparently several countries around the world have blacklisted them because of adverse health consequences resulting from their products about which they have lied or concealed the truth. Apparently, they are big"—this is all quoted. "Apparently they are big into switching labels and the like."

Do you know if the FDA has ever looked into that e-mail or the allegations as to whether it is true or accurate or not?

Mr. BAKER. Mr. Chairman, I am familiar with the Helm issue. I am not familiar with the details of the case. I wasn't anticipating testifying on that.

Mr. UPTON. Would you be able to respond——

Mr. BAKER. Yes, sir.

Mr. UPTON. [continuing] in writing back to the committee within a week or so and we will share it with both sides?

Mr. TAYLOR. Absolutely.

Mr. BAKER. That will not be a problem.

Mr. UPTON. Here is a copy of the e-mail for you. I think that will be helpful.

Again, I appreciate you coming up today. Next time we would like to have your testimony so I can take it home a night or two before the hearing.

I want to compliment the staff on both sides for making sure that we were prepared and have been able to walk through this, and the members that were here today, and we look forward to having you again——

Mr. BAKER. Mr. Chairman.

Mr. UPTON. [continuing] to talk about the progress, Dr. Henney—and to talk about the progress that's been made from today knowing some of the details that we were alerted to.

Do you have a closing statement that you would like to make?

Mr. BAKER. Mr. Chairman, I would like to thank you and thank the committee for having us here today and for listening. There are a number of issues clearly that have to be resolved. There are problems. We fully acknowledge that. The one thing I do is solve problems. That's part of my job. I am here today because I am the new guy on the block and these people report to me. And I am prepared to take the hits for that. We will correct these problems to the extent we can, and you will know what our problem areas are and what our resource needs are. It's our duty to let you know.

Mr. UPTON. Well, we want to make sure that you succeed. It will require some follow-up. Thank you.

[Whereupon, at 1:20 p.m., the subcommittee was adjourned.]

[Additional material submitted for the record follows:]

PREPARED STATEMENT OF JOHN T. RIETZ, PRESIDENT AND CHIEF EXECUTIVE OFFICER, ISOTAG TECHNOLOGY, INC.

Mr. Chairman: My name is John Rietz and I am President and CEO of Isotag Technology Inc., with offices in Texas, Florida, and New Mexico. Thank you for the opportunity to submit this statement for the record and I commend you for convening this important hearing.

ISOTAG Technology, Inc. provides the world's leading covert identification products and services. Our patented technology, which was originally developed at the Los Alamos National Laboratory (LANL), offers economic solutions for anti-counterfeiting, anti-diversion, product liability protection and quality and process control management.

ISOTAG's unique combination of technology, detection, data management, decision support, and enforcement will effectively and conclusively solve the counterfeiting of bulk drugs. We believe that our comprehensive, complete solution offers the best assurances for the purity of medicines taken by all Americans.

ISOTAG's products and services include:

1. Molecular Tagging—ISOTAG provides a unique, covert molecular fingerprint, introduced during the drug manufacturing process, which provides forensic proof of authenticity and purity.
2. Inviable Inks—ISOTAG recently acquired invisible ink technology, which was developed by Eastman Chemical Company, called Clircode. This patented technology operates in the Infrared area of the spectrum, which overcomes some of the inherent problems associated with invisible UV inks. Clircode can be applied at multiple points in the drug distribution process such as packaging, boxes, labels or holograms and are detected via hand-held readers and cameras.

Clircode, in conjunction with the molecular ISOTAG, provides cost-effective and complete protection against all potential counterfeiters and diverters.

I would be most pleased to present our state-of-the-art technology and a proposal providing a solution to the current bulk drug counterfeiting problem to the committee at your convenience. Additionally, we would be pleased to make a presentation to the appropriate officials at the Food and Drug Administration to assist in their efforts to stop the flow of counterfeit drugs coming across our borders.

In conclusion Mr. Chairman, I want to thank you again for the opportunity to participate in this important hearing. I would be pleased to respond to any questions you might have as you continue in your efforts to protect the health of all Americans.

To: Jon Hunt@DEIO@FDAORAHQ, Gary Pierce@DEIO@FDAORAHQ
From: Gary Pierce@DEIO@FDAORAHQ
Certify: N
Subject: Fwd: more on international labeling
Date: Thursday, November 13, 1997 at 11:51:55 am EST
Attached: None

- - - - - - - - - - - - - - Original Message - - - - - - - - - - - - - -

To: Ron Chesemore@ACRA@FDAORAHQ, Jerry Vince@ORO@FDAORAHQ, Gary Pierce@DEIO@FDAORAHQ, Thomas Gardine@IO@FDAORAHQ, Jack Mitchell@INVESTIGATIONS@FDAOC, Jason Brodsky@OPA-BMS@FDAOC, Walter Batts@OIA@FDAOC, John Lucas@OIA@FDAOC, Marilyn Veek@OIA@FDAOC
From: Mary Pendergast@IO@FDAOC
Date: Thursday, November 13, 1997 at 11:26:05 am EST
Attached: None

To all: I have from a very good source some interesting information I want to share with you relating to the DEG/Haiti/China situation, and international trade generally (some of this may already be known to some of you):

1) Helm, AG is the parent company for Vos. Vos had taken the contaminated glycerin from Metall-Chemie and shipped it to Haiti. Earlier we learned that before Vos shipped the drums of glycerin to Haiti, Vos had taken a sample of the drums, but we were told that Vos never tested the sample, and then destroyed the sample.

The information I received is that Vos took the sample, then shipped the drums, but then Vos actually did the testing on the glycerin, learned that it was very sub-standard, but Vos didn't recall the drums or warn Parval (even though the drums had not even reached Haiti by the time Vos knew that the glycerin was not USP glycerin). There is a criminal prosecution for murder being developed by the Netherlands government against Helm/Vos.

2) Helm/Vos are notorious in other parts of the world for not telling the truth about what they are shipping. Apparently several countries around the world have blacklisted them, and refuse to accept any shipments of any products from them, because of adverse health consequences resulting from their products, about which they lied/concealed the truth. Apparently they are big into switching labels and the like.

3) There will be futher big time press interest in the Helms/Vos story as an example of the shady world of international trading, and how no one can really know what they are getting, etc.

Obviously, it would be nice, when this next round of press hits, to be able to say that we have systems in place so bad guys like Helms/Vos don't ship here, and that everything that comes into this country is true and properly labeled or subject to criminal prosecution, etc etc etc.

Do we have an application integrity program for brokers/shippers? Do we need one?

Call me if you have any questions. In the meantime, please do not share this information with anyone outside of the agency, even with other agencies, and share it only selectively inside the agency.

Thanks. Mary

DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
July 25, 2000

The Honorable FRED UPTON
Chairman
Subcommittee on Oversight and Investigations
Committee on Commerce
House of Representatives
Washington, D.C. 20515-6115

DEAR MR. CHAIRMAN: Thank you for your interest in the safety of pharmaceutical drugs in the United States (U.S.). This is in follow-up to the Subcommittee's June 8, 2000, hearing on counterfeit bulk drugs. Mr. Dennis Baker, Associate Commissioner for Regulatory Affairs at the Food and Drug Administration (FDA or Agency) was asked to provide information for the record.

We have restated the questions in the order they were asked, followed by our response.

1. Mr. Stupak—Provide information on the status of actions taken regarding the importation of non-pharmaceutical grade radioisotopes and the manufacturing and sale of radioactive diagnostic drugs under the guise of the practice of pharmacy.

FDA has been evaluating how to treat the compounding of radiopharmaceuticals in light of statutory changes mandated by the Food and Drug Administration Modernization Act of 1997 (FDAMA), Public Law 105-115. Specifically, FDAMA added a new Section 503A to the to the Federal Food, Drug, and Cosmetic Act (the Act) which creates exemptions for compounded products from certain provisions of the Act. Section 503A(e)(2), however, provides that Section 503A does not apply to radiopharmaceuticals.

We expect to issue responses to a number of inquiries on this matter very soon, and we will, at that time, be able to provide the Committee with more detailed information regarding our enforcement policy.

2. Mr. Bryant—Why is FDA not working with the Customs Service on counterfeits and will FDA reconsider that position?

FDA has worked with the U.S. Customs Service (USCS or Customs) on specific counterfeit drug investigations in the past, and will continue do so in the future when warranted.

The Flavine counterfeit investigation and prosecution, completed in 1996, was a long-term joint investigation worked by FDA's Office of Criminal Investigations (OCI) and Customs. The reason OCI has not worked with Customs on counterfeit bulk drugs since 1996 is because no substantive information identifying a counterfeit bulk drug entering the U.S. has been brought to the attention of OCI or Customs since that time.

OCI has a cooperative working relationship with Customs, including a Memorandum of Understanding with Customs providing for all OCI agents to be cross-designated as Customs officers. OCI currently is working a number of on-going investigations with Customs involving unapproved and counterfeit finished human drugs and adulterated or misbranded medical devices and foods. The Customs Service in recent testimony before the Committee on May 25, 2000, stated, "Customs also has several ongoing investigations involving U.S. persons operating foreign pharmaceutical websites. All of these investigations are being worked jointly with the FDA's OCI. The Customs Office of Investigations has a great working relationship with FDA investigators."

OCI is willing to work with Customs on a criminal investigative task force, if warranted. However, the establishment of a task force is predicated on identifying a large number of specific criminal violations that are occurring and the need to respond to those violations with the resources of a number of agencies. A good example of this is the USCS High Intensity Drug Trafficking Area Task Force at the Dulles International Mail Facility where OCI is represented.

In the case of counterfeit bulk drugs, no large number of specific criminal violations has been identified. Accordingly, FDA has concluded that a joint standing task force with Customs for counterfeit bulk drug investigations is not warranted at this time.

If credible new information regarding counterfeit bulk drugs is obtained, criminal investigations will be initiated in the appropriate venue and worked jointly with Customs. The Committee should be assured that when information is received concerning suspect counterfeit activity, OCI will work closely with Customs and other law enforcement agencies to conduct a thorough investigation, and OCI will provide FDA officials with any information developed regarding possible public health implications.

FDA also is providing additional training to its import inspection cadre that includes an effort to improve our effectiveness in working with Customs' field personnel. During the period of June 19 through July 14, 2000, approximately 80 FDA field and supervisory staff involved with imports each received 36 hours of advanced training, including instruction from Customs personnel on that agency's statutory authority, regulations and operating procedures. Another 40 staff is receiving the training during the week beginning July 24, 2000. The training included strategic problem-solving exercises in working with Customs personnel to jointly address problems encountered in the field regarding the importation of counterfeit bulk drugs.

3. Mr. Bryant—Please respond to the following five questions.

A. Does FDA favor posting OCI agents in Europe and Asia regarding counterfeits?

The permanent posting of one or more OCI agents overseas has been considered a number of times over the last decade, but the Agency has, in each instance, concluded that the large additional expense would outweigh the potential benefits. FDA has requested funding in its FY 2001 budget that would be partially used to support a criminal investigator assigned to Interpol. This would support and facilitate OCI's criminal investigations and provide the Agency with a point of contact for international police intelligence information related to terrorism.

B. Does the Agency favor a joint FDA/industry effort regarding counterfeits?

Yes, we do. FDA already meets with the security directors of the various pharmaceutical manufacturers to discuss ways to more productively cooperate through the exchange of information and the provision of information relevant to investigations.

FDA believes our relationship with industry on the issue of counterfeiting should be improved, and the Agency will enhance our relationship with top management of the pharmaceutical industry, particularly those individuals who oversee the security and regulatory affairs departments. This was an agenda item for the most recent meeting of the Field Drug Committee, which is a group of senior Office of Regulatory Affairs and Center for Drug Evaluation and Research managers who make decisions related to FDA's drug inspection program.

FDA has already met with top officials of Johnson & Johnson, DuPont Pharmaceuticals and representatives of CEFIC (the European Bulk Drug Industry). We will also meet with the New Jersey Health Counsel, which consists of top officials of the pharmaceutical industry in New Jersey, on July 27, 2000, to discuss our anti-counterfeiting initiative and encourage their cooperation in this effort.

As noted in Mr. Baker's testimony of June 8, 2000, manufacturers are already required to test and validate the safety, purity and consistency of the active pharmaceutical ingredients used in their products. We are exploring some new actions that manufacturing firms might be able to take in order to better detect counterfeits.

C. Do you favor developing new systems in FDA to identify counterfeit drugs and other unapproved or illegal drug that enter the country?

Yes, we do, and the Agency has already begun this process. FDA has begun to implement certain recommendations in the 1999 Draft Plan, such as evaluating a trace-back procedure for bulk products and a procedure for the submission of information from industry regarding suspicions that bulk products are counterfeit, substandard, or from outside approved sources.

In addition, FDA has re-established an Agency-wide Working Group on counterfeit bulk drugs, in order to further refine FDA's strategy on bulk drug importation and to develop additional systems to prevent, deter and interdict the importation of counterfeit drugs.

D. Submit plan on implementation of new technologies such as taggants.

The new Working Group on counterfeits, described above, is considering this issue and the possible use of taggants or similar technologies will be discussed with industry as part of our joint FDA/industry efforts described above.

E. What can the Committee and Congress do to help FDA?

FDA is making a full assessment of its needs and areas for improvement in handling counterfeit bulk drugs. We will submit a detailed plan of action to the Committee, as requested by Chairman Upton, in the near future. As requested, we will address our resource and/or legislative needs in detail at that time.

4. Mr. Strickland—Provide information on whether allowing China into the World Trade Organization (WTO) would hamper FDA's ability to regulate counterfeit drug products from that country.

FDA's laws and regulations apply to covered imported products without regard to the products' country of origin or the status of the importing country as a member of the WTO or any other international organization. China's accession to the WTO Agreement would not change the application of FDA's requirements to products originating in China.

5. Mr. Upton—Respond to the issues raised in the November 13, 1997, e-mail from Mary Pendergast, former Deputy FDA Commissioner, regarding the Helm import company.

The referenced e-mail was written during the time period following the 1996 contamination of glycerin used in medications distributed in Haiti, in which FDA assisted the Haitian government and conducted investigations in Europe and China to determine the source of the suspect glycerin. The e-mail from Ms. Pendergast to the Commissioner of Food and Drugs expressed concern about the part that Helm/Vos played in the glycerin incident.

The 1996 investigation in Haiti disclosed that the suspect glycerin (contaminated with diethylene glycol (DEG)) used in production of liquid acetaminophen was shipped from China to the Vos warehouse in the Netherlands and then to Haiti. In July 1996, FDA completed an investigation at the Vos facility in Europe and at a European trader, who purchased the glycerin from China. Information concerning these investigations was provided to the appropriate European authorities for further investigation of the incident.

In September 1996, FDA conducted an investigation at Helm New York, Piscataway, New Jersey, in follow-up to the glycerin problem in Europe and Haiti. The investigation disclosed that Helm New York handled limited quantities of glycerin and a private laboratory had tested the latest lot of glycerin received by the establishment. Since September 1996, other investigations have been completed at the Helm New York facility to address issues concerning the establishment's importation of active pharmaceutical ingredients.

In 1997, FDA completed investigations in China in an attempt to determine the source of the glycerin and cause of the contamination with DEG. The investigations disclosed that the glycerin shipped to Haiti had been manufactured in China. We were unable to determine the point at which the contamination of the glycerin with diethylene glycol had occurred. During the investigations, we obtained a copy of a telefax from the European trader to the Chinese trader who handled the glycerin, which stated that the purity of the glycerin in the suspect lot was "53.9% instead of 98% min."

FDA has taken other steps to insure the safety of imported glycerin used by finished dosage form pharmaceutical manufacturers including issuing an import alert for glycerin from China and investigating entries of imported glycerin from sources other than China. We continue to periodically monitor glycerin exported to the U.S.

6. Mr. Upton—Does FDA believe it has the authority to require importers to identify the ultimate consignee.

Yes, FDA believes it has the authority to require importers to identify the ultimate consignee. We are now evaluating how best to establish such a requirement without placing an unnecessary burden on industry or inhibiting trade.

Thank you for making this information a part of the public record. We look forward to working with the Committee on our mutual goal of protecting the American public from the importation of counterfeit or otherwise dangerous drug products from abroad.

Sincerely,

MELINDA K. PLAISIER
Associate Commissioner for Legislation

cc: The Honorable Ron Klink
Ranking Minority Member
Subcommittee on Oversight and Investigations
Committee on Commerce
House of Representatives

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
August 10, 2000

The Honorable FRED UPTON
Chairman
Subcommittee on Oversight and Investigations
Committee on Commerce
House of Representatives
Washington, D.C. 20515-6116

DEAR MR. CHAIRMAN: This letter is in response to the Subcommittee's June 8, 2000, hearing, regarding counterfeit bulk drugs. As discussed at the hearing, the Food and Drug Administration (FDA or the Agency) was asked to- report back to

Subcommittee with a plan to improve the detection and interdiction on imported counterfeit and substandard Active Pharmaceutical Ingredients (APIs).

Directly following the hearing, the Agency re-established a Counterfeit Drug Working Group (Working Group) to explore issues of imported counterfeit and substandard drugs, FDA's import operations and foreign drug inspection program. over the past two months the Working Group had numerous meetings to devise a workable plan to assess the extent of the counterfeit drug problem in the United States (U.S.). The Agency also has contracted with a private firm to assess the status of FDA's import Information Technology (IT) and to explore the most efficient way of connecting databases to share information more readily with FDA's field inspectors. Since the June 8 hearing, the Working Group has had under development a plan for detecting these products to better ensure that the public is protected from potentially hazardous drug products.

The report will outline the Agency's plans for better handling imported counterfeit and substandard APIs and finished drugs. The plan also will outline FDA's training program for import inspectors on counterfeit drugs as well as the initial use of the Establishment Evaluation System (EES) database by import inspectors. These latter programs have been developed since the Subcommittee hearing.

The additional resources, personnel and funding that FDA believes is necessary to fully carry out our responsibilities for inspecting foreign drug manufacturers and to increase the surveillance of foreign APIs and finished drugs are under review by the Working Group. Because the scope of this evaluation needs to encompasses both the Agency's domestic and foreign operations, as well as the operations of various FDA Centers, parts of this analysis are preliminary in nature. The Agency looks forward to providing more specific information on our funding needs relating to personnel and technology in the future, once a complete assessment is made and appropriate review has occurred.

A. PROBLEM STATEMENT AND SUMMARY OF ACTIONS

The increase in international trade has had an impact on the ability of FDA to cope with the volume of regulated products, including APIs. As Mr. Dennis E. Baker, Associate Commissioner for Regulatory Affairs (ORA), stated at the June 8 hearing, while FDA believes that the quality of drugs in this country is high, the Agency takes very seriously any allegations regarding the counterfeiting or adulteration of drug products. The Agency realizes that more can be done to help ensure that imported APIs and finished drug products meet the requirements of the Federal Food, Drug, and Cosmetic (FD&C) Act.

Diminishing or flat-lined resources, coupled with the increasing volume of APIs from overseas, have stretched personnel and resources so thinly that FDA has been struggling to fulfill the program mandates in these areas. Policing the global drug marketplace to deter or interdict imported substandard drugs is a daunting task, given the resources made available to FDA.

In response to this challenge, the Agency has developed a risk-based approach to foreign drug inspection. The Center for Drug Evaluation and Research (CDER) developed a four-tiered approach to perform surveillance inspections of firms that FDA has not been able to inspect. At the present time FDA is only able to inspect Tier I (Official Action Indicated, or OAI, inspection follow-up) and Tier II (sterile bulks, finished drugs and aerosols) firms. The required pre-approval inspections are being conducted in accordance with the Agency's mandate under the Prescription Drug User Fee Act. Resources are the primary factor limiting the Agency's ability to undertake additional inspections. The Working Group is looking at these issues and discussing how to best utilize current resources and what it would cost, as discussed in the June 8 hearing, to perform the inspections in all tiers of the CDER risk-based system.

As stated previously, a Working Group has been re-established to explore the issues raised in the June 8 hearing. The Working Group consists of representatives from many Agency programs. These include the Office of Criminal Investigations (OCI), the Division of Import Operations and Policy (DIOP), the Office of Enforcement, the Forensic Chemistry Center (FCC), the Division of Federal-State Relations (DFSR) and the Division of Information Systems, and, Division of Emergency and Investigational Operations, all of which are components of ORA, and the Offices of Compliance within the Center for Drug Evaluation and Research (CDER) and the Center for Veterinary Medicine (CVM).

The Working Group is in the process of assessing the effectiveness of the regulatory tools, compliance programs, staffing and procedures that already exist within the current statutory construct to monitor imported APIs. The Agency already has implemented the following actions:

- FDA has contracted with a private IT contractor to assist the Agency in examining its existing technology and data. FDA has charged the firm with recommending ways to integrate its systems and expedite the availability of important data to the consumer safety officers and inspectors that are responsible for monitoring imports at the nation's ports of entry.
- As mandated in the Food and Drug Administration Modernization Act of 1997, FDA has drafted a final rule requiring foreign establishments whose products are imported or offered for import into the U.S. to register with FDA and to identify a U.S. agent. once in place, the rule will provide for the collection of information needed to establish an accurate Official Establishment Inventory for foreign drug firms.
- ORA's DIOP has engaged their counterparts at U.S. Customs Service (Customs) to assist in putting Customs house brokers and importers on notice that they must declare the proper manufacturer of their imported products. Accurate information will assist FDA with the difficult task of finding imported counterfeit or unapproved APIs and preventing their use in finished drug products.
- ORA has developed a plan to establish a cadre of expert investigators and chemists that would be stationed in strategic high volume API import locations across the country. This plan will require more resources.
- FDA has extended access to the EES database to the three FDA Districts handling the vast majority of imported APIs. Training for FDA import inspectors already has been accomplished and accounts have been established.

The Working Group is studying many other suggestions and proposals that have been put forward. The initiatives noted above, which will be discussed in greater detail, represent a significant first effort at improving our foreign inspections, drug surveillance, and import operations to better protect the American public from the threat of imported counterfeit APIs.

B. AGENCY INITIATIVES CURRENTLY UNDERWAY

In June and July 2000, FDA conducted three Import Enforcement training courses for FDA import personnel including Compliance Officers, Consumer Safety Officers, and Consumer Safety Inspectors. Approximately forty students attended each one-week course representing in total about half of all persons assigned to field import operations. FDA and Customs attorneys jointly developed the course curriculum at the request of FDA's Division for Import Operations and Policy. The instruction course included training in Strategic Problem Solving (SPS), a Customs training module developed specifically to facilitate the targeting, investigation and prosecution of willful violators. Each course included a facilitated workshop after the pattern of SPS. In each class, two of the problems involved specific imported API counterfeiting fact patterns. Facilitated brainstorming by the field personnel focusing on the imported counterfeit API threat produced numerous ideas for strategies in detecting, preventing and interdicting counterfeit imported APIs. The Working Group is assessing these proposals for viability.

FDA's FCC and Customs have agreed to explore methods to better leverage their respective resources in the investigation and analysis of suspect counterfeit products. The FCC is hosting the first meeting in their forensic laboratory on August 10, 2000, to demonstrate FDA's current forensic capabilities and strategies. The two Agencies will explore better means to coordinate their efforts by granting access to analytical data and equipment and cross training in methodologies and emerging forensic techniques. The FCC will interface directly with Customs' laboratories to share information on analytical procedures FDA's forensic experts use to detect unapproved and counterfeit APIs. The Working Group has placed a high priority on developing with Customs a unified approach for interdicting counterfeit drugs.

Under FDA's Compliance Program 56002F, "APIs", FDA requests information relating to API characterization at the conclusion of current good manufacturing practices (CGMP) inspections. The FCC collates this information into a database for the development of a library of authentic APIs. These data will be used as one tool for identifying suspect counterfeit APIs during FDA's operations. The Working Group is currently assessing the most practical means for making FCC's data readily available for FDA personnel during import entry examinations and foreign and domestic drug inspections.

The FCC has scheduled additional API targeted inspections at various importers and finished dosage manufacturers throughout the U.S. Additional hands-on training is planned for investigators in other strategic locations. In February 2000, the FCC briefed Mr. Baker of the potential threat of imported counterfeit APIs. Consequently, Mr. Baker authorized and funded FCC's efforts to conduct targeted API inspections at the importer and domestic finished dosage manufacturer levels. With these funding increases the FCC conducted six targeted API inspections. Three of these are importers of foreign APIs, two are domestic finished dosage manufacturers and one is a domestic animal drug manufacturer. The FCC inspectors are now reviewing imported API documents and samples of product, labeling, packaging schemes and certificates of analyses. At each of these inspections, the FCC worked with local FDA district drug investigators to detect suspect API shipments through product and records examinations.

Based on unverified data from the Operational and Administrative System for Import Support (OASIS) that was originally supplied by Customs house brokers when various drug entries were filed, there are approximately 4600 firms that appear to be non-inspected foreign drug manufacturers. The Agency is reviewing the OASIS data to develop an import alert for foreign establishments that appear to have exported to the U.S. an API that is normally used to manufacture a finished dosage form which requires an approved application. A preliminary assessment by FDA's CDER, Office of Compliance, thus far, has identified forty-six firms in China and Hong Kong and eleven firms in India that appear to have exported to the U.S. in 1999. These firms have never been inspected by FDA and appear to be exporting a misbranded drug to the U.S. The Agency is developing an import alert for these firms and expects to be able to add to this list as the OASIS data is further evaluated. The final phase of the analysis of the OASIS data will be to identify firms FDA has not inspected but which are referenced in approved human and animal drug applications. The human drug firms will be evaluated using a risk-based analysis stratified into one of four tiers, incorporated into FDA's surveillance list, and subsequently scheduled for inspection.

Previously, Philadelphia District Office participated in a pilot that involved an evaluation of imported APIs by cross-referencing drug manufacturing data submitted by importers with CDER's EES database. EES contains information tracking new drug applications (NDAs) and animal new drug applications (ANDAs) and relates those applications to approved sources raw materials, including APIs. FDA is extending the EES pilot. This represents new information previously unavailable to import inspectors. Field access to EES combined with a proposed new use of labeling exemptions under Title 21, *Code of Federal Regulations* (CFR) part 201 could result in the development of a monitoring, surveillance and enforcement model for all APIs and other drug components. On July 10, 2000, FDA trained investigators and compliance officers from New York, New Orleans and San Juan District Offices (DO) in the use of EES as a supplemental tool for evaluating the admissibility of APIs from foreign sources for use in manufacturing an NDA or ANDA. The trainees have received EES accounts and are familiarizing themselves with the use of the database in evaluating Customs entry data and providing additional training in their home districts to other import personnel. This EES training is an extension of the pilot to the three districts that handle the largest proportion of API Customs entries.

The Working Group anticipates combining EES with other strategies could result in: (1) a marked increase in the prevention of non-drug manufacturing file referenced APIs being used in the manufacture of application drugs, (2) a procedure for tracking APIs and drug components from port to end-user destination to deter diversion within U.S. market, (3) an increase in opportunity for field exams of APIs upon entry for evaluation of authenticity, (4) the development of leads for OCI and "for cause," foreign producer, importer, and domestic end-user inspections, and (5) the development of intelligence on international distribution channels of counterfeit and unapproved drugs.

The Agency has placed the import industry on notice regarding the requirement to supply the Agency with accurate data regarding the identity and location of the manufacturer of imported drugs. Upon review of the notices made to the community over the last several years it became apparent that these requirements had been made clear to importers and brokers through notices issued on January 29, 1999, and March 24, 2000. Recently, the Agency again posted an updated version of its requirements on the Internet with links to and from FDA's import operations pages. Additionally, on July 28, 2000, a Customs Automated Broker Interface (ABI) Administrative message was issued to all filers with a reference to the Internet site containing these requirements and a physical mailing address where a filer may request a hard copy from the Agency. A copy of the July 28, 2000, ABI notification is enclosed.

C. ADDITIONAL STRATEGIES AND IDEAS FOR HANDLING IMPORTED COUNTERFEIT AND UNAPPROVED DRUGS/APIS

The Agency has been developing and implementing strategies for assessing the scope of the threat of imported counterfeit APIs to the U.S. consumers. The Working Group has identified three major operational components for evaluation: foreign inspections, domestic inspections and import operations. In order for FDA to ensure the integrity of APIs from place of manufacture to place of use and sale in the U.S., and to assure those drugs are manufactured and held in conformance with good manufacturing practices (GMPs), information from these three components must be integrated and made readily available. Furthermore, when the Agency intends to conduct a foreign inspection, relevant data obtained from the Agency's domestic operations must be available to the foreign domestic operations must be available to the foreign inspectors for verification or development of additional evidence where suspect activity has been identified. These interfaces require a more comprehensive and integrated use of IT to increase the speed and accessibility of relevant data. An additional evaluation by the Agency is underway to determine how the industry could participate in combating the potential threat of counterfeit drugs internationally and domestically.

1. IT Proposals and Solutions.

On July 1, 2000, ORA engaged the services of an IT contractor to assess the Agency's overall IT needs and to propose changes which will accomplish the following goals.

The IT contractor was charged with determining the information that FDA import inspectors need to fully assess admissibility of all FDA regulated commodities. The contractor consulted with import inspectors and compliance officers with expertise in FDA and Customs laws and regulations, GMPs and IT import applications.

The contractor has used a comprehensive data gathering and assessment framework to analyze the functional process, infrastructure, and IT systems used by ORA to support import operations. The data gathering involved a workshop with the import operations staff, onsite visits to relevant FDA centers and to a DO, system demonstrations, interviews with system and infrastructure managers, and review of documentation on ORA operations provided by FDA. Analysis involved an iterative approach to development of processes, issues and recommendations. Each iteration consisted of a team analysis, followed by a group session to compare and validate each team's assessment. To identify the most appropriate technology, the contractor conducted extensive technology scanning, arranged for vendor presentations, reviewed FDA plans and discussed possibilities with FDA staff.

The contractor also was charged with developing strategies for converting information currently on paper into an electronic format form. This information is necessary for the import inspector to make a more efficient admissibility decision. The contractor was asked to develop short and long term proposals for integrating the FDA's databases and for creating a secure electronic environment in which large amounts of data may be securely transmitted and accessed by authorized Agency personnel. These proposals are to take into account anticipated growth of the regulated industry, the dramatic increase of cross-center products entering interstate commerce, and the need for flexibility to maximize the Agency's enforcement and surveillance efforts.

Finally, the contractor has been charged with assisting the Agency in assessing the viability of countermeasure technology to detect and deter import violations.

The Agency expects a final report from the contractor in August 2000.

2. Joint Industry/Agency Efforts.

Members of the Working Group conferred with the FDA's Field Drug Committee (FDC) on counterfeit API issues. The FDC historically has maintained networks with drug industry personnel and trade associations and has utilized these relationships for furthering the important message of health and safety through consistency in GMP compliance. The FDC has agreed to assist the Working Group in developing avenues through which industry could join forces with the Agency in combating counterfeits in the market place.

Beyond this initial approach through the FDC, the Agency is exploring additional routes for encouraging and receiving intelligence on counterfeit drugs in the world market. Historical experience in prior counterfeit API investigations has demonstrated that foreign API manufacturers whose products are being counterfeited can provide substantial assistance in developing tests for authenticity and intelligence regarding suspected counterfeiting operations. The Agency is aware that intelligence gathering from the trade is a critical element to successfully identifying suspect counterfeits in the market.

In connection with the IT contractor's evaluations, the Agency may be able, with appropriate funding, to establish a secure Internet environment to encourage manufacturers to provide confidential and sensitive information to the Agency. Depending upon the intelligence received, the Agency may be able to identify sources of counterfeits or substandard products or evidence of other related criminal activity.

3. Foreign Inspection Component.

Since 1990, the Agency has shifted resources from domestic to foreign programs to increase presence in the foreign drug manufacturing market place recognizing the shift in global markets. For the Fiscal Year (FY) 2001 foreign work plan, the Agency will focus on the manufacturers that have not been inspected as identified through the analysis of unverified OASIS data. Resources necessary to fully implement the four-tiered inspection system are being evaluated by the Working Group and will be provided when available.

The foreign drug inspection program for the current FY is on track for accomplishing approximately 450 foreign inspections. This represents more foreign inspections than the Agency has ever accomplished in a single year. Because the program continues to be primarily application driven, the priorities associated with the product approval process have impacted on our ability to conduct drug surveillance inspections. For FY 2001, ORA is projecting approximately 500 foreign drug inspections. This projection includes substantial increases in drug surveillance inspections, which should result in increased coverage of firms in tiers three and four. The Agency is attempting to accomplish this increase through reallocation of existing resources. This will result, however, in a reduction in domestic inspection programs.

Due to resource restrictions, the Working Group is examining other avenues for developing evidence that a foreign firm is complying with GMPs. Although there is no true substitute for a physical GMP inspection, there may be critical production or validation records which, through an Agency review, may provide a minimum level of assurance that the firm is aware of and making efforts to comply with GMPS. The Working Group is examining modification of the procedures for submitting Drug Master Files.

For instance, under current Agency regulations, validation of a drug manufacturer's process is not required for obtaining an approval, however, it is required prior to shipment in interstate commerce. Under the current paradigm, due to inadequate resources, the Agency often cannot verify a foreign manufacturer's validation records prior to the first shipment to the U.S. Requiring the production of such records in conjunction with or prior to shipment of drugs to the U.S. may permit the Agency to review the firm's validation. Overall such a review may assist the Agency in focusing its resources toward firms that appear to lack adequate control and validation systems. Such a program could be extended to the importation of over-the-counter drugs under the same authority.

Compelling the production of such GMP required documents for imported drugs may require FDA rule making. Such a program would assist the Agency in leveraging its human resources to complement foreign inspections,

4. Domestic Inspection Component.

The Working Group has identified a need for integrating the foreign and domestic inspection programs together with the Agency's import operations. For instance, the Working Group is recommending the use of "Process Mapping" or "System Re-engineering" within ORA to identify areas of internal procedural overlap and disconnects that may contribute to the lack of information exchange among these inspection programs. The IT contractor is expected to assist in assessing the viability of an integrated data system which will permit access and data submission based upon personnel role definitions.

Current instructions for performing domestic finished dosage manufacturer GMPs have not focused on authenticity of warehouse API stock. The inspector will generally track a randomly selected API or other raw material from receipt through quarantine and quality control testing, into production, verifying that proper batch numbers are recorded throughout the process. Assuming that this review demonstrates no discrepancies, these aspects of the manufacturing processes are presumed to be within the limits of GMPs. Therefore, the Working Group is evaluating the need to add components to and modify domestic inspection procedures to provide comprehensive coverage of APIs during inspections of end users.

5. Import Operations Component.

FDA's DIOP is responsible for providing policy guidance to the field relating to import procedures, overseeing the development and operation of the Agency's Import Alert system, and for maintaining the Agency's OASIS system.

The Working Group is reviewing DIOP's procedural and system operations and is assessing the Agency's personnel and equipment needs to better monitor U.S. ports of entry. During the June 8 hearings, Customs designated over 300 ports of entry. OASIS data indicates that approximately 100 ports have seen entries of APIs. FDA has a notable presence in over 40 ports. The ports where FDA conducts the bulk of its work represent those through which the vast majority of drugs enter.

The Working Group is considering whether current FDA or Customs authority would sustain a restriction on which ports of entries certain commodities, such as drugs, may be offered for import based upon a health and safety assessment. Other approaches might be available to accomplish a similar effect. For instance a proposal to restrict entry of certain commodities to certain times of the workday or week rather than by geographical criteria.

The Working Group reviewed Import Alert 68-09, which covers over 50 veterinary APIs. Although this alert was originally issued in 1993, it remained largely unutilized due to inadequacies in FDA's product coding system. Consequently, CVM, CDER and ORA components are reviewing a Working Group proposal to merge all human and animal drugs into a common "drug" FDA product code. This will align the CVM product code system with CDER's system enabling criteria to be set in OASIS to make CVM import alerts more effective. Because many APIs have application in both human and animal drug industries, the Working Group is considering consolidating human import APIs into Import Alert 68-09.

6. Possible new use of drug labeling requirements.

The Working Group is examining the development of a new use of the drug labeling requirements found at 21 CFR Part 201. CVM's Import Alert 68-09 currently addresses imported API drug labeling noting "[b]ulk new animal drug substances labeled for further manufacturing or processing, which do not bear any indications for veterinary use, may be misbranded under section 502(f)(1) [of the FD&C Act] if they are intended for veterinary use or for further processing as animal drugs." The Import Alert continues "21 CFR 201.122 exempts a drug from adequate directions for use when labeled for further manufacturing and processing and when used to manufacture a new animal drug, which is covered by an approved application.

". . . 21 CFR 201.150 exempts a drug, which is intended to be further processed or manufactured, from adequate directions when it is shipped under the terms of a written agreement which, if followed, will assure the finished product is not adulterated or misbranded." This Import Alert was revised on July 12, 2000, and has been the basis of Working Group discussions for extension of the drug labeling regulations to control imported APIs and drug ingredients generally.

7. Proposal for assessing the existence or extent of imported counterfeit and substandard drugs.

ORA has proposed a plan for assessing the extent of the potential threat that imported counterfeit and unapproved APIs may pose to the health of the unsuspecting American consumer. This plan would require an increase in ORA's current staff, equipment and supplies for forensic analyses, and operational funds for domestic and foreign inspections that would target imported APIs. The plan could generate leads for criminal and civil enforcement actions and provide concrete factual and analytical data upon which the Agency could plan its next course of action.

The proposal consists of establishing a team of experts to detect counterfeit and substandard APIs. This specialized team would be stationed in strategic locations identified by high import or manufacturing activities. They would conduct focused API inspections of domestic and foreign manufacturers, importers, and conduct forensic analyses of resulting samples. The overall resource requirement for this plan includes additional full-time equivalents and funding for equipment, domestic travel and operational costs. Foreign inspection costs would increase these funding needs. ORA is assessing the viability of the proposal.

8. Possible International Collaboration.

The Working Group is investigating whether collaborations with foreign governments could increase the Agency's ability to verify the existence and the compliance status of manufacturers, shippers, repackers or relabelers of drugs of other countries. Such collaboration would involve counterpart foreign government agencies authenticating the source and quality of APIs imported into the U.S.

9. Possible Security Measures.

The Working Group is engaged in discussions with the Customs' Applied Technology Division which has considerable experience in tracking shipments within U.S. commerce to verify and document cargo diversion. The Working Group will evaluate the currently available technology in terms of levels of surveillance capabilities, cost of equipment and implementation.

The Working Group has asked the IT contractor to explore low cost security devices for use by foreign manufacturers such as chemical taggants in labeling, glue, ink or packaging materials to detect suspect counterfeit drugs. The Agency is considering a wide array of available technology including encrypted bar code technology in labeling and Certificates of Analysis containing manufacturing information already submitted by the foreign manufacturer through a secure web-based environment. Other possible solutions include radio frequency tags for detection during examinations at ports of entry.

The Working Group will continue its assessment of the extent of the counterfeit drug problem in the U.S. The strategies outlined above will be further developed and enhanced. Additionally, other potential strategies will be examined.

Thank you for your continued interest in these important issues. We hope this information is helpful, please contact us if you have further concerns or questions.

Sincerely,

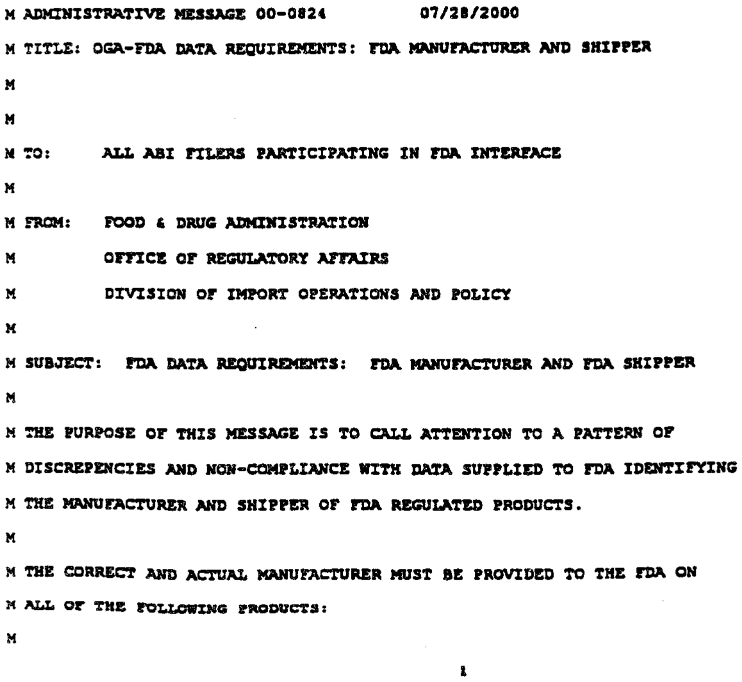
MELINDA K. PLAISIER
Associate Commissioner for Legislation

Enclosure

cc: The Honorable Ron Klink
Ranking Minority Member
Subcommittee on Oversight and Investigations
Committee on Commerce

The Honorable Thomas J. Bliley, Jr.
Chairman, Committee on Commerce

The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce



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M ADMINISTRATIVE MESSAGE 00-0824          07/28/2000

M TITLE: OGA-FDA DATA REQUIREMENTS: FDA MANUFACTURER AND SHIPPER

M

M

M TO:     ALL ABI FILERS PARTICIPATING IN FDA INTERFACE

M

M FROM:   FOOD & DRUG ADMINISTRATION

M         OFFICE OF REGULATORY AFFAIRS

M         DIVISION OF IMPORT OPERATIONS AND POLICY

M

M SUBJECT:  FDA DATA REQUIREMENTS:  FDA MANUFACTURER AND FDA SHIPPER

M

M THE PURPOSE OF THIS MESSAGE IS TO CALL ATTENTION TO A PATTERN OF

M DISCREPENCIES AND NON-COMPLIANCE WITH DATA SUPPLIED TO FDA IDENTIFYING

M THE MANUFACTURER AND SHIPPER OF FDA REGULATED PRODUCTS.

M

M THE CORRECT AND ACTUAL MANUFACTURER MUST BE PROVIDED TO THE FDA ON

M ALL OF THE FOLLOWING PRODUCTS:

M

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M       ALL HUMAN DRUGS

M       VETERINARY DRUGS

M       BIOLOGICS

M       MEDICAL DEVICES

M

M THIS ALSO APPLIES TO ANY FOOD PRODUCT REQUIRING PROCESS FILING WITH
FDA
M BEFORE MARKETING IN THE UNITED STATES.  ALL OF THESE PRODUCTS REQUIRE

M EVIDENCE THEY WERE PRODUCED IN A FACILITY WHICH HAS REGISTERED OR
LISTED
M ITS PRODUCTS WITH FDA.

M

M SUPPLYING THE CORPORATE HEADQUARTERS, TRADING COMPANY, BROKERAGE OR

M OTHER INTERMEDIATE SUPPLIER AS THE MANUFACTURER IS NOT ACCEPTABLE FOR

M THESE PRODUCTS.  SHIPMENTS IDENTIFIED IN THIS MANNER WILL BE DELAYED

M IN PROCESSING AND MAY BE DETAINED UNTIL CORRECT INFORMATION IS
PROVIDED.
M FURTHER, CONTINUED USE OF INCORRECT FIRM DATA, AS WELL AS OTHER DATA

M ERRORS, MAY RESULT IN FILER REMOVAL FROM ELECTRONIC ENTRY CLEARANCE.

M

M PLEASE WORK WITH THE IMPORTER TO CORRECTLY IDENTIFY THIS FIRM DATA

M TO FDA.  BAD DATA MAY RESULT IN FAILURE TO KEEP VIOLATIVE PRODUCTS OUT
OF
M UNITED STATES COMMERCE, INCORRECT FIRMS PLACED ON IMPORT DETENTION,

M INCREASED SAMPLING AND EXAMS OF AN IMPORTER'S ENTRIES, AND OTHER

M ENFORCEMENT ACTIONS.

M

M FDA'S POLICY ON DATA REQUIRED FOR THE "FDA" MANUFACTURER AND SHIPPER

M CAN BE REVIEWED AND THE TWO PAGE FORMATTED DOCUMENT CAN BE OBTAINED
FROM
M THE FOLLOWING INTERNET ADDRESS:

M

M       HTTP://WWW.FDA.GOV/ORA/IMPORT/AUTOMATEDSYSTEM.HTML

M

M A COPY OF THIS INFORMATION MAY ALSO BE OBTAINED FROM THE FDA AT

M THE FOLLOWING ADDRESS:

M       FOOD AND DRUG ADMINISTRATION (FDA)

M       OFFICE OF REGULATORY AFFAIRS

M       DIVISION OF IMPORT OPERATIONS AND POLICY

M       5600 FISHERS LANE, HFC-170

M       ROCKVILLE, MD  20857
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FDA Manufacturer and FDA Shipper
Data Transmission Requirements

The FDA Manufacturer and FDA Shipper are two of the FDA data elements currently used for automated entry screening in FDA's Operational and Administrative System for Import Support (OASIS). Every effort must be made to provide the actual FDA Manufacturer and FDA Shipper as defined below.

FDA Manufacturer: The FDA Manufacturer is the site-specific location where the product is manufactured, produced, or grown.

FDA Shipper: The FDA Shipper is the actual shipper of the product identified on freight bills or bills of lading and is often the same as the USCS invoicing party.

Many FDA regulated products, e.g., Low Acid Canned Foods (not limited to those products packed in metal "cans"), Medical Devices, Human and Veterinary Drugs, and Biologics ALWAYS require evidence they were produced in a facility which has registered, licensed and/or listed its products with FDA. For these products, the site-specific location must be submitted as the FDA Manufacturer. The name and address of a corporate headquarters, "trading company", or other intermediate supplier is not acceptable. [1]

Some food products (including raw agricultural, aquacultural, or fishery products) do not have mandatory registration, listing, or licensing requirements. If the actual site-specific manufacturer (or manufacturers in a multi-source lot) is (are) identified on the entry documents that information MUST be transmitted to OASIS. Often the manufacturer and shipper information provided on an invoice is not the same as information provided on the bill of lading. Care should be taken to provide the most accurate information available.

Agricultural co-ops and other consolidators are often transmitted as the FDA Manufacturer and FDA Shipper. These firms may be appropriately used to identify the FDA Shipper. They should only be transmitted as the FDA Manufacturer when entry documents do not identify the actual FDA Manufacturer (manufacturer/producer/grower) and the filer has made an unsuccessful good faith effort to determine the actual FDA Manufacturer. When detained shipments are identified with a consolidator as the FDA Manufacturer, the entire shipment will be detained, regardless of the actual FDA Manufacturer(s). If the consolidator is put on Detention Without Physical Exam, related shipments from that firm, regardless of the FDA Manufacturer(s) involved, will be placed on Detention Without Physical Exam.

FDA Manufacturer and FDA Shipper
Data Transmission Requirements

Summary

1) If the FDA registration/licensing/listing requirement applies to an imported product and/or its manufacturer, the actual site-specific FDA Manufacturer must be supplied. If a given invoice line contains the same product from several manufacturers, the line must be broken out into separate FDA lines and the FDA data elements must be submitted separately for each FDA line.

2) If there is no FDA registration, listing, or licensing requirement, but the actual site-specific FDA Manufacturer information is readily available to the filer (from the entry papers or otherwise) it must be submitted. [1]

3) If a product (such as a raw agricultural commodity) does not require registration, listing, or licensing, and the actual site-specific FDA Manufacturer information is not available, after making a good faith effort to determine same, the filer may instead transmit the FDA Shipper in lieu of the FDA Manufacturer. NOTE: In this case the FDA Country of Origin remains the country where the actual site-specific FDA Manufacturer is located; the filer may be able to determine this from the invoice "Product of —" statement. If, after due diligence, the filer cannot determine the FDA Country of Origin, the Customs Country of Origin may be substituted in its place.

4) While it is technically permissible to transmit the shipper or consolidator under the situations described in example three above, every effort must be taken to provide the actual FDA Manufacturer. Failure to do so may result in the wrong firm being added to an FDA Import Alert and future shipments could be subject to Detention Without Physical Exam when another firm is actually responsible for the violation.

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[1] The only exception to this data requirement is where a valid MOU or other binding agreement between FDA and a foreign governmental agency directs otherwise.

COUNTERFEIT BULK DRUGS AND RELATED CONCERNS

TUESDAY, OCTOBER 3, 2000

HOUSE OF REPRESENTATIVES,
COMMITTEE ON COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 10:05 a.m., in room 2322, Rayburn House Office Building, Hon. Fred Upton (chairman) presiding.

Members present: Representatives Upton, Cox, Burr, Bryant, Bliley (ex officio), Waxman, Strickland, and Dingell (ex officio).

Also present: Representative Coburn.

Staff present: Alan Slobodin, majority counsel; Anthony Habib, legislative clerk; and Chris Knauer, minority counsel.

Mr. UPTON. Good morning, everyone. Today the subcommittee continues its oversight and investigation of counterfeit bulk drugs and other issues related to imported drugs. On June 8 of this year this subcommittee held a hearing on FDA's failure to take adequate actions concerning imported bulk drugs. Several key findings emerged from that hearing.

One, for the first time the FDA publicly disclosed that it knew 4 years ago that the deaths of Americans were in fact linked to a counterfeit bulk drug. Two, in 1996 the FDA and Centers for Disease Control determined that 89 Haitian children died from taking cough medicine made with poisonous antifreeze traced to China but labeled as glycerine. The FDA's follow-up investigation of the Haitian cough medicine case uncovered shipments of suspected glycerine that made their way into the United States. The FDA linked toxic adverse reactions to 155 American patients on an antibiotic called gentamicin sulfate made by a Chinese bulk manufacturer, Long March Pharmaceutical. Even with a system of safeguards such as FDA inspections and manufacture testing, the Long March bulk drugs still reached and harmed unsuspecting American patients.

The FDA had little or no information on about 4,600 firms that had shipped bulk drugs into this country, including 623 from China and 409 in India. This lack of information showed the inadequacies in FDA's information systems and the real risks of uninspected firms shipping counterfeit or substandard drugs into the U.S. .

Since the June 8 hearing there have been more key findings in developments on the counterfeit drug import front. Because of the committee's investigation the FDA magazine so far identified at least 46 firms in China and 11 firms in India that appear to have exported misbranded drugs to the United States in 1999 and have never been inspected. The FDA recently advised committee staff that as many as 242 firms worldwide appear to have shipped misbranded drugs to the United States in 1999 and yet have never been inspected.

In July committee staff visited the port of Laredo, Texas and on the U.S.-Mexican border to learn about the U.S. Customs Service and FDA controls of commercial and personal imports of prescription drugs. The staff visit showed the lack of controls over Mexican pharmacies and the wide availability of suspicious counterfeit or substandard prescription drugs imported from Mexico.

Last month committee investigators accompanied Dennis Baker, FDA's Associate Commissioner for Regulatory Affairs, to China and India to observe FDA inspections of bulk drug firms and to gather additional information on issues related to the counterfeit drugs. Here are some of the important findings from that trip:

Committee staff obtained evidence that Chinese firms are secretly manufacturing drugs that are still under U.S. patent. The firms market these violative drugs using secret price lists.

In another interesting counterfeiting example a Chinese pharmaceutical company is marketing products allegedly as food, but these products actually contain the active ingredients of Viagra. It is difficult to track counterfeiting in China because counterfeiting factories use a day shift for making a legitimate drug and sometimes a night shift for the counterfeit version. Some local government authorities are complicit in the counterfeiting and thwart operations that could expose these practices. Chinese government authorities who are not corrupt often lack the resources to investigate. Another difficulty is the inability to track product flow because distribution in China is very complicated.

Two developments that make China a bigger time bomb of drug counterfeiting are these: China's joining the WTO and Internet sales. But India may be the biggest counterfeiting problem because of the lack of patent laws and the lack of centralized regulatory control of the pharmaceutical industry. According to FDA inspectors, the plants in China and India visited by the committee staff seem to be representative of most of the drug plants inspected in China and India. But if that is so, these plants use outdated technology and procedures no longer used in the West.

In addition, it is difficult to believe that these plants can remain compliant since these plants are normally operating outside of U.S. regulations when they manufacture for their domestic market and are not pressured by environmental or other safety laws such as firms here in the United States. There are major obstacles to FDA foreign inspections being able to assure the same safety standards as domestic inspections. Unlike domestic inspections, FDA foreign inspections in China and India cannot use samples of microbiological testing because the samples would lose their integrity by being shipped for testing to a U.S. lab. Unfortunately, no field testing is available.

Even when an FDA inspection teams includes a Mandarin speaking FDA inspector, the language barrier remains a major problem in China because there are difficulties in translating technical terms and the firm's interpreter can sometimes lack that scientific knowledge. Where the firm's interpreter has scientific training, these interpreters sometimes tend to go beyond interpreting and suggest answers or provide leading questions to employees.

Also, FDA inspection teams try to work efficiently and split up to look at different parts of the firm. As a result FDA inspectors often are still relying on the firm's interpreter even when another FDA inspector on the team in fact knows the language.

Beyond some of the new information obtained by the committee there has been another important development: Legislation on an appropriations bill that would change FDA laws to ease reimportation of U.S.-made prescription drugs. Much of the debate has focused on safety. These concerns are a reflection of the investigative work of this subcommittee in the 1980's, and today. This subcommittee will continue its oversight work to ensure that the FDA can control the current flow of drug imports and that the FDA not implement schemes that would in any way jeopardize the safety requirements of drug imports.

Last, since the June 8 hearing the FDA has reported back to the subcommittee on actions and strategies to improve its scrutiny of imported drugs. The Department of Justice has reported back to Chairman Bliley on proposals to strengthen investigation and prosecution of crimes involving counterfeit drug imports. We will hear in some detail at this hearing about these actions, plans and proposals from the FDA and the Department of Justice.

We talked a lot at the June 8 hearing about what was wrong with the FDA. Today I want to mention something right with the FDA. His name is Dennis Baker, and he is FDA's Associate Commissioner for Regulatory Affairs. He has had a very tough job, testified for FDA at the June 8 hearing. But from what I have been told by staff, he I know is a dedicated public servant who is genuinely committed to improving the FDA. And Dr. Henney, I hope you will send a strong and loud message of support for him and for the upgrading of information technology that he seeks and that the FDA badly needs. Welcome, today's distinguished witnesses.

We are particularly honored that Raymond Kelly, U.S. Customs Service Commissioner, is joining us today. Certainly I want to extend a very warm welcome to the FDA Commissioner, Dr. Jane Henney, who is making her first appearance before this subcommittee. I look forward to discussing these vital issues and working with you to find effective solutions. I yield to——

Mr. COBURN. Mr. Chairman, as a member of the full committee and a former member of the O&I Subcommittee, I would ask unanimous consent to participate in this hearing.

Mr. UPTON. Is there any objection to that? Hearing none, the gentleman is allowed.

Mr. DINGELL. I'll defer to the chairman.

Mr. UPTON. Mr. Bliley, the chairman of the full committee.

Chairman BLILEY. Thank you, Mr. Chairman. You held a hearing last summer on imported counterfeit drugs and today we will look at some very serious questions about FDA's ability to assure that all drugs manufactured here or abroad meet safety requirements. Congress is about to enact permanent changes to the Food, Drug and Cosmetic Act as part of the agricultural appropriations bill.

I regret that these kind of policy changes are being made without action in the Commerce Committee. Relaxing the laws governing the importation and reimportation of prescription drugs into the United States will have far-reaching consequences, some potentially dangerous. Unfortunately, a full vetting of this issue has not occurred. I am very concerned that the Congress is legislating changes to a public health law that may be unwise and may erode the gold standard that exists for the quality and efficacy of drugs consumed by Americans.

I think all my colleagues in the administration would agree it is completely unacceptable to have two safety standards for the drugs that Americans consume, one for the drugs made here and a lower one for imports. When it comes to safety, there should be no compromises. This committee has been vigilant on drug safety. Imported or reimported drugs should meet the same rigorous standards. Avoiding this double standard is important because in many cases drug imports can not be assumed as safe as U.S. drugs.

Under my authority investigators from this committee last month went with the FDA to China and India to see firsthand the bulk drug plants and the problems with inspecting them. While China and India have a wealth of human labor and scientific talent, these drug plants lack resources and systems to assure safety. The plants that the staff observed had major problems meeting such basic safety requirements as clean water, good ventilation, and methods to avoid contamination. In the opinion of the investigators and the FDA inspectors, these kinds of plants could not exist in the United States because they would be unable to compete.

Beyond these plant visits, investigators also obtained information and evidence related to fraud and counterfeiting that are a reality in the international pharmaceutical trade. FDA already cannot assure against the double standard because of weak import controls and inadequate information systems.

Prompted by this committee's investigation, the FDA has reviewed its records on drug imports and found that 242 firms may have shipped misbranded drugs to the United States in 1999 and have never been inspected. The total of 242 includes at least 46 firms from China and 11 from India.

FDA must upgrade its enforcement and information systems to assure the safety of imported drugs. In addition to these improvements, there must be effective criminal enforcement against fake drug imports.

After the June 8 hearing, I wrote to Attorney General Janet Reno about the Justice Department's view on improving ways to investigate and prosecute crimes related to counterfeit drug imports. In response to my request, the Department has suggested some legislative proposals such as requiring certain records as part of a foreign drug inspection and ensuring extraterritorial application of the Food, Drug and Cosmetic Act. These proposals seem reasonable in concept and I support them. I would be pleased to have the committee work with the FDA and the Justice Department on developing legislative language.

As the reimportation of prescription drugs is eased, this committee has worked and will continue to work to strengthen protections for consumers against imports of fake drugs. Today's hearing to get more information on the problem and on proposed solutions and action is yet one more example of this committee working to protect consumers.

I welcome today's witnesses and look forward to the testimony.

Mr. UPTON. Thank you, Mr. Chairman. Mr. Dingell.

Mr. DINGELL. Mr. Chairman, I thank you. I have a longer statement which I ask to be inserted in the record.

Mr. UPTON. Without objection, all members of the subcommittee will be allowed to introduce and offer their statements in their entirety.

Mr. DINGELL. Mr. Chairman, it is amazing to me how many times this Congress must relearn the same lesson, how little we profit from it and what messes we get ourselves into by failing to address the real underlying problem. I know there is a tremendous drive to allow reimportation of drugs or to allow importation of drugs and pharmaceuticals and other things in a more expedited easy fashion. This I think is in good part because my colleagues to some degree on both sides of the aisle, but mostly on the majority side, have found that the people are fed up with the fact that a lot of Americans are, (A) paying too much and, (B) that our senior citizens are not able to get prescription pharmaceuticals because they simply cannot afford them, and of course with some of the witchcraft that is coming forward on the other side of the aisle about how we are going to pay for prescription pharmaceuticals by enriching HMOs means that my colleagues on that side have urgent need of something to shelter them against public criticism.

In the 99th Congress, this committee looked at reimportation of prescription pharmaceuticals. We had a long bipartisan report. We found a number of things. We found, for example, shipments of fake pharmaceuticals. We found unsafe packaged pharmaceuticals. We found counterfeits. We found adulterated antibiotics from places like China. We found prescription pharmaceuticals that had been repackaged under unsafe conditions that had been stored under unsafe and under conditions which created deterioration of the prescription pharmaceuticals and which put Americans at risk.

So we passed the basic legislation to which we are inquiring today, the PDMA, which required that the prescription pharmaceuticals be imported through licensed manufacturers. That was because the Congress was, quite frankly, too stupid and too tight to properly fund these programs and because OMB saw to it that Food and Drug didn't have the money that they needed to do the job and didn't have the resources and the number of people.

Now, with a growing trade in prescription pharmaceuticals from places like China, we are going to expand the amount that comes in. The chairman just made, I thought, a very sapient observation in which he pointed out that there is desperate need to see to it that Food and Drug has the resources to do the job that they have to. We aren't seeing to it with that situation, and I intend to ask a few questions about it.

Now if you think that you are limiting this only to subjects like prescription pharmaceuticals and things which will come in, you are entirely in error, because we are talking about aerosol inhalers, we are talking about pre-mixed-injection solutions, we are talking about ointments and creams, auto injectors, power inhalers, topical gels, injection solutions, inhalation solutions, pediatric solutions, capsules, prefilled syringes, and a wide array of other things, including syrups and nasal sprays.

Now, if you are talking about having Food and Drug catch somebody at the border when they have the array of shipments that they have in, you are going to find that, (A) they can't do it and, (B) they can't paw through to find out whether these substances are in fact safe, whether they are deteriorated, whether they are manufactured under good manufacturing conditions as required by our law or whether they are doing other things. In short, you are setting yourself up, if you pass legislation easing reimportation or easing importation, to a situation where you are looking at a fine calamity and some fine killings of Americans and making Americans ill because you are not doing the job that you should in terms of seeing to it that Food and Drug has the resources to address these problems now.

I would just call to your attention one little thing, where Food and Drug some years back had a scare over Chilean grapes. They pulled the whole Food and Drug administrative and enforcement mechanism and they sent them to the ports to look and see what was going on. They found, I think, three grapes that had cyanide in them. But the result of this mess was that there was a prodigious lack of enforcement of all parts of the foods and drug law because they didn't have either the people or the resources without this particular scare to do the job that they needed to do.

So I look forward with a great deal of interest to what we uncover today. I intend to ask about the resources and to try and recall for the benefit of those who have not learned this lesson, as I had to learn it back in the 99th Congress, about what happens when you turn loose an agency without proper resources, charge them with protecting the American people and then find that they cannot do the job that they have to do.

I think that this is particularly subject to criticism when we do this in order to avoid criticism for failing to pass proper legislation to address the problems of our senior citizens and having prescription pharmaceuticals made available to them at a reasonable cost.

In any event, this will be an interesting hearing. We will try and see to it that it is lively and that all participate. In the meantime if anybody has got any loose time I have an excellent statement which deals with these matters and other matters in greater detail, which I hope will be helpful to the Chair, to the committee and to the Congress in terms of understanding the mess in which we are injecting ourselves.

Thank you, Mr. Chairman.

[The prepared statement of Hon. John D. Dingell follows:]

PREPARED STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. Chairman, I have long been concerned about counterfeit, substandard, misbranded, and adulterated drugs entering this country from abroad. Previous investigations conducted by this Subcommittee more than a decade ago ultimately led to the passage of the Prescription Drug Marketing Act (PDMA), which added measures to protect consumers from potentially dangerous foreign drug sources. But protecting consumers from questionable and dangerous drug products manufactured abroad remains a formidable challenge.

I remain concerned that the Food and Drug Administration (FDA) has yet to develop a suitable framework for protecting the public in the face of potentially greater risks. The agency still remains alarmingly behind in inspecting those firms that send drug products here, and it still lacks the ability to track and measure the global counterfeiting problem. What is more troubling is that significant new responsibilities could soon be placed on an agency that is already underfunded and struggling to meet its current mandate.

Mr. Chairman, FDA is supposed to inspect firms for Current Good Manufacturing Practices (CGMPs) before they are approved to ship a drug product into the United States. Yet at the last hearing, it was disclosed that approximately 4,600 foreign drug firms may have shipped products to the U.S., yet were never inspected by the agency. FDA now tells us that the figure is lower, but they still cannot tell us what it is. That inability does not instill confidence.

The lack of this kind of information stems from the agency's reliance on an incomplete and outdated information technology system called OASIS. We have asked the agency to address the shortcomings of this system for years, but FDA has failed. While FDA is again trying to fix this system by hiring yet another outside contractor, the fact remains that the agency still cannot efficiently generate data critical to its foreign inspection efforts.

A workable system for tracking who sends what and when to this country, and whether such firms meet U.S. good manufacturing practice requirements, must be implemented, and soon. Commissioner Henney should immediately determine the agency's information technology requirements, and then finish the job.

Meanwhile, as FDA continues to struggle with this problem, new inspection demands are piling up. Although we cannot determine the exact size of the foreign inspection backlog, we know that one exists and it appears considerable.

What is worse is that in the coming years increased inspection demands will only grow. For example, staff was told that next year, as many as 10 to 15 new facilities requiring an FDA inspection could emerge in China alone. For this single country, FDA would have to significantly increase its inspection efforts from the previous year, which would represent a significant resource expense to the agency. Multiply this across the globe and the ensuing problem becomes obvious.

How will we expect the FDA to keep pace with such demand when it is already falling behind? Further, if the agency cannot keep up, what will the effect be on the safety of the nation's drug supply? These are critical questions that must be asked and properly addressed. What is also important is that we ask these questions in the context of the larger debate now taking place regarding drug pricing. That is because the outcome of that debate could have profound consequences on how the agency does its job, and how it allocates resources.

While it is known that I have a number of safety concerns regarding most of the re-import proposals, I also have concerns that we are on the verge of asking an already overstretched agency to do significantly more. I remain skeptical whether we will adequately fund FDA, or even if it is technically prepared and capable of doing the job. I cannot think of a time when FDA was not struggling for resources, nor do I recall that the agency did a particularly good job at stopping adulterated and counterfeit material from reaching our shores before the Prescription Drug Marketing Act went into effect.

Policing the world's drug supply is an expensive endeavor. Yet, while we agree that foreign inspections are a critical component to safeguarding the nation's health, we still do not adequately fund them. Why? If we are going to hold the FDA responsible for being the world's drug cop, shouldn't we provide it with the necessary resources to do the job competently?

Let me conclude by saying that I believe that drug counterfeiting is a very real problem that will likely only grow worse in the future. The world's drug supply is every bit as vulnerable to dangerous counterfeiting today as when I first began the investigation more than 15 years ago that ultimately led to the Prescription Drug Marketing Act. And while I have a great deal of respect for my friends at the FDA that continually protect us from that threat, I do believe the agency is slipping behind in meeting its mandate. I would think long and hard about whether, in the near future, we want the agency to take on even greater responsibilities, before we have first addressed what is now broken.

I look forward to hearing from today's witnesses, and with that, I yield back.

Mr. UPTON. Thank you. Recognize the vice chair of the subcommittee, Mr. Burr.

Mr. BURR. Thank you, Mr. Chairman. Welcome, Commissioner Henney. Mr. Chairman, before I make my written remarks, let me associate with the chairman of the committee and the ranking member of the committee with the concern that I personally hold after a 2½-year commitment through the FDAMA legislation at a time where we worked aggressively, every member of this committee, to protect the gold standard that we recognize existed at the Food and Drug Administration and the dismay that we go through today with an effort to open up the market to a flow of drugs in a way that we can't, I believe, fulfill the commitment to meet the same standard.

It is somewhat of an amazement that it bypassed this committee, that the effort is stuck into an appropriations bill and that individuals responsible within this government for the safety and efficacy of our pharmaceuticals have been supportive of this effort for reimportation and importation. I have tried to stay focused on this hearing because it deals with counterfeit drugs. It is somewhat ironic that we would highlight the problem that exists in America and at the same time walk into another room and talk about how to expand the risk to us of a current problem.

After reviewing Commissioner Henney's testimony, I am pleased to see that the FDA listened to several of our suggestions at the June 8 hearing and has moved forward with some important initiatives. However, several statements in the testimony do raise some questions. One, given that the importers were notified on January 29, 1999, March 24, 2000, July 20, 2000 and July 28, 2000, that they must provide the FDA with the identity and location of the drug import manufacturers, it concerns me that you have not provided us with any compliance data on the requirement today. The first notice was given over 20 months ago.

Two, as one of the authors of FDAMA, it disheartens me to see that a final rule on a requirement included in FDAMA has just been sent for approval to the Office of Management and Budget. It is very important for foreign establishments whose products are imported or offered for import into the U.S. to register with the FDA and identify a U.S. agent. It should not have taken FDA 3 years to issue a rule on this part of the FDAMA legislation. You state that the Office of Criminal Investigations is working on a number of ongoing investigations with Customs involving unapproved and counterfeit finished human drugs. I am curious to know how many investigations are included in a number after all the years the FDA just spoke about the potential threat posed by counterfeit drugs.

Four, the Prescription Drug User Fee Act requires preapproval inspections of manufacturing facilities. Why are there by FDA's count 242 uninspected foreign manufacturers that are exporting products to the United States of America? The bottom line in this issue is consumer safety. It should be as it relates to the debate on counterfeit drugs, it should be as it relates to any debate about a stream or flow of pharmaceuticals, be them finished or bulk, to this country and I hope that never changes.

I thank the chairman. I yield back.

Mr. UPTON. Thank you.

Mr. Bryant.

Mr. BRYANT. Thank you, Mr. Chairman. I too, as my colleague from North Carolina did, wish to associate myself with the remarks of our chairman of the full committee as well as the ranking member in terms of the concern that we all have regarding the availability of prescription drugs to our population as well, and specifically to our senior citizens.

I would differ with those on the committee who raise complaint about this Congress passing for the first time ever a prescription drug benefit for our senior citizens, something again that has never happened. And while it may not be the perfect bill, and rarely do we initially pass a perfect bill out of the House, it is a good start. It goes a long way down the road in providing universal coverage.

It is a voluntary bill, one that doesn't make you get into the program if you don't want to, one that provides very good access to this benefit and at the same time provides a catastrophic type coverage for people out there who have extremely large bills. I think, importantly, it offers this, to coin a Washington phrase, sooner than later, this is something our senior citizens in particular don't need to wait years to begin receiving this type of benefit.

I would specifically thank our chairman of this subcommittee, Mr. Upton, for a very timely hearing. I think in terms of providing an opportunity to have the FDA in at this time as well as Customs and Justice to talk about the importation issue is a wonderful opportunity, given several things, the Internet and sales and things like that that are just overwhelming Congress in so many ways. The Internet itself, sales of prescription drugs and other things would be one of those, but so many other times I think that the Internet and the technology that is emerging, particularly in the pharmaceutical industry, are overwhelming Congress's ability to keep up and enact legislation and to regulate to the extent those are necessary. Just deciding whether we need to regulate or legislate sometimes is a difficult decision itself.

But I do look forward to the testimony of this very distinguished panel. Obviously the issue of the day is the importation and even the legislation that my colleague in North Carolina referred to, the riders to the agriculture appropriation bills that permit this. The legislation that protects the safety and the efficacy of drugs was put in place for a reason.

There is a concern now, again with the rising cost of drugs, that we look at ways to lower those costs. This was one of the things that has been passed out of the House, but again not without controversy. I do look forward to the statements from the panelists on those opinions. And given the events of the last week with the approval of the drug RU-486, I am sure that might come out in some examination, because that obviously has very broad implications, too, in this arena of reimporting drugs into the country and the safety, which I think we all agree is foremost in the minds of all the people in this room today as well as I suspect in Washington also.

With that said, I would be happy to give back my time, but again my appreciation for your very timely hearing today.

Mr. UPTON. Thank you.

Mr. Waxman.

Mr. WAXMAN. I have no opening statement. I welcome our witnesses. I look forward to their testimony. I will reserve all my comments until we get into questions. But I also want to commend the

FDA for its decision last week on RU-486 and so many other things where I think it is doing a good job. You should hear sometimes from us and we acknowledge that.

Mr. UPTON. Well thank you. At this point we are prepared to have the first panel testify. We are honored to have the Honorable Jane Henney, Commissioner of the Food and Drug Administration, with us today; the Honorable Raymond Kelly, Commissioner of the U.S. Customs Service; and Ms. Patricia Maher, Deputy Assistant Attorney General, Civil Division, from the Department of Justice. Welcome.

As you may know, your statements in their entirety are made as part of the record. We would appreciate it if you might be able to summarize that in about 5 minutes or so. And as you may know, testimony before in subcommittee traditionally has always been under oath. And do any of you have objection to us taking your testimony under oath?

Ms. HENNEY. I don't have objection to taking it under oath, but I would like to affirm rather than swear, affirm rather than swear as you give the oath.

Mr. UPTON. Okay.

Mr. DINGELL. That is proper.

Mr. UPTON. Do any of you wish to be represented by counsel as well? If not, if you would stand.

[Witnesses sworn.]

Mr. UPTON. You are now under oath, and, Dr. Henney, we will start with you. Thank you and welcome.

TESTIMONY OF HON. JANE E. HENNEY, COMMISSIONER, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DENNIS E. BAKER, ASSOCIATE COMMISSIONER, REGULATORY AFFAIRS; HON. RAYMOND KELLY, COMMISSIONER, U.S. CUSTOMS SERVICE; AND PATRICIA L. MAHER, DEPUTY ASSISTANT ATTORNEY GENERAL, CIVIL DIVISION, DEPARTMENT OF JUSTICE

Ms. HENNEY. Thank you. Good morning, Mr. Chairman, members of the committee. I am Jane Henney, Commissioner of Food and Drugs. I appreciate the opportunity to be here today to discuss our efforts to detect and prevent the introduction of counterfeit bulk drugs into the drug supply of the United States and specifically to report on our actions since your hearing on this matter in June. A more comprehensive report of these activities is in my statement, and I appreciate your placing that in the record.

FDA believes that the quality of drugs in this country is high, but we must take very seriously any allegations regarding the counterfeiting or adulteration of drug products. The agency agrees with the committee's assessment that more can and should be done to help ensure that imported bulk drugs or active pharmaceutical ingredients in finished products meet the requirements of the Federal Food, Drug and Cosmetic Act.

The agency has been developing and implementing additional strategies for assessing the scope of the threat of imported counterfeits and moving forward with activities already under way. Let me begin by providing the committee with an update on the five initiatives FDA announced at the time of the June hearing.

No. 1, additional funds were allocated to the Forensic Chemistry Center for sampling, analytical work and assessments of APIs gathered through targeted inspections of importers. With these funding increases, the Forensic Center has conducted 20 targeted API inspections, including 9 at importers of foreign APIs, 10 at domestic finish dose manufacturers, and one at a domestic animal drug manufacturer. The Forensic Center inspectors are now analyzing the information obtained during these inspections to determine whether additional follow-up by district officers, investigators or our Office of Criminal Investigations is warranted.

Two, make the Forensic Center API data base available electronically to all field investigators by January 2001. This, as you recall, is a data base that currently contains information or fingerprints on 330 APIs that have been collected and chemically analyzed by the Forensic Center. This information is one important tool that FDA can use to more quickly identify whether or not a product is authentic or counterfeit. The technology necessary to make the Forensic Center's API data base available to all of our field and port and drug inspectors is being developed and planned. We do expect to have the system in place by January 2001.

Three, expand the Philadelphia pilot nationwide by the end of 2000. The Philadelphia pilot, as you will recall, allowed inspectors to retrieve additional drug approval data from the Establishment Evaluation System, or EES, data base maintained by the Center for Drug Evaluation and Research in about 3 to 4 minutes on any API entry. Rapid access to this information increases the probability of confirming authentic sourcing of APIs.

The pilot was a success and access to this system has been expanded to three FDA districts handling the vast majority of APIs, New York, New Orleans, and the San Juan district offices. Currently we are completing plans for the additional technology upgrades in the training for field personnel necessary to expand the program to the rest of our districts, which we will complete early next year.

Four, put all importers on notice that they are required to provide the name of the foreign manufacturer upon entry into the U.S. and that the entry of their products into the U.S. will be contingent upon it. The agency has placed the import industry on notice regarding the existing requirement to provide FDA with accurate data regarding the identity and location of the manufacturer of imported drugs. On July 20 of this year, we posted an updated version of these requirements on the Internet with links to and from FDA's import operations pages. And on July 28 a Customs systems administrative message was issued to all files with a reference to this Internet site containing these requirements. Compliance with this requirement is assessed as the agency carries out routine filer evaluation. Customs has informed FDA that these types of reporting failures may be the basis for Customs civil actions. This information will be useful to the agency in better defining and identifying a universe of foreign manufacturers shipping to the U.S.

Five, require domestic manufacturers to provide information to FDA when they discover that the bulk materials they receive are substandard, ineffective or appear not to be from the approved source. As you may know, the committee proposed this idea to the agency last year. We are proceeding with efforts to develop a proposed regulation that would establish this requirement.

I would be pleased to also note actions that we have under way or other actions we have taken, including foreign registration. We have cleared and forwarded to OMB the final rule requiring foreign establishments whose products are imported or offered for import into the U.S. to register with FDA and to identify a U.S. Agent. This rule will be effective 6 months after the publication of the final rule, and it will provide us the collection of information needed to establish an accurate official established inventory.

We have reestablished our working group and this group has spent 3 months exploring a full range of issues regarding imported counterfeit and substandard drugs.

On the important issue of information technology needs assessment, it was one of the greatest concerns at the June hearing, for the agency does lack a well-integrated IT system, particularly with respect to regulation of drug imports, but as it relates to our other information systems as well. We have had a contractor undertake a study. Their report has recently been received by the agency and we are currently reviewing both their recommendations and their resource estimates. We have also begun very aggressive cross-training with the U.S. Customs Service in June and July. We've conducted three import enforcement training courses for our own personnel. This is a course that has been jointly developed by FDA and Customs, who have developed the course and teach it. And it focuses on the interplay between FDA and Customs enforcement measures, strategic problem solving, administrative procedures and international agreements, and one-half of the training is in Customs law and regulation. We are extending this course to additional field personnel and we will be joined by other members of the Customs Service as well.

The other cooperative efforts we have with Customs include our memorandum of understanding with a cross-designation of our OCI agents as Customs officers and we are working on a number of ongoing investigations with Customs regarding unapproved and counterfeit finished human drugs, medical devices, and foods.

We have also had very aggressive discussions with Customs' Applied Technology branch about the use of countermeasures to detect counterfeits and track shipments when warranted. We have also been active in the international arena, which I would be glad to spend time discussing with you if you would like in the questions and answers. And we are also working with Customs on the leveraging of science and technology. We have met to explore methods to better leverage our respective resources in this manner.

We had hosted at the Forensic Center a meeting on August 10 with Customs officials to look at ways to use analytical data and equipment and cross-train in methodology and emerging forensic techniques. With respect to an import alert, we have been working with the issue of identifying foreign API manufacturers shipping to the U.S. who have not been inspected. As many members have cited, this data has enabled us to produce a list of 242 manufacturers in 36 countries that appear to have exported to the U.S. in 1999 but have not been inspected. Today we have issued an import alert for these uninspected foreign drug establishments. We have also had additional strategies for handling imported counterfeit unapproved drugs and APIs under consideration, which I will be happy to discuss during the questions and answers.

Mr. Chairman, in June you asked us what additional resources, personnel and funding may be necessary to fully carry out our responsibilities for inspecting foreign drug manufacturers and to increase the surveillance of foreign APIs and finished drugs. The agency has long recognized that we need additional resources in the area of post-market surveillance, which would encompass many of the activities I've discussed. In just the past 2 years, fiscal year 1999 and fiscal year 2000, the President's budget included $25.8 million and $39.3 million, respectively, for post-market surveillance activities. Neither of these requests was funded. The lack of new funding and absence of increase for our core operations reduces the numbers of FTEs available to perform the agency's critical post-marketing activities.

At this time only preliminary estimates have been made of these resource requirements, as the scope of this evaluation needs to encompass both the agency's domestic and foreign operations as well as the operations of the various FDA centers. Once we have assessed these needs, we will look forward to working with you and the other Members of Congress to assure FDA has the tools it needs to do our job for the American public.

Mr. Chairman and members of the committee, I want to assure you that all of us at FDA remain concerned about any possibility that counterfeit or otherwise unsafe drugs may find their way into the American drug supply. We will remain vigilant as we refine and improve our programs and procedures that we use to ensure the availability of safety medications for consumers. We appreciate your continued interest in these issues, and I will be happy to answer questions.

[The prepared statement of Hon. Jane E. Henney follows:]

PREPARED STATEMENT OF HON. JANE E. HENNEY, COMMISSIONER OF FOOD AND DRUGS

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Jane E. Henney, M.D., Commissioner of Food and Drugs, Food and Drug Administration (FDA or the Agency). I appreciate the opportunity to be here today to discuss our efforts to detect and prevent the introduction of counterfeit bulk drugs into the drug supply of the United States (U.S.), and specifically, to report on our actions since your hearing on this matter in June.

As we stated in our testimony at your June 8 hearing, FDA believes that the authenticity and quality of drugs in this country is high, but we must take very seriously any allegations regarding the counterfeiting or adulteration of drug products. The Agency agrees with the Committee's assessment that more can and should be done to help ensure that imported bulk drugs or Active Pharmaceutical Ingredients (APIs) and finished drug products meet the requirements of the Federal Food, Drug, and Cosmetic (FD&C) Act. Since June 8, the Agency has been developing and implementing additional strategies for assessing the scope of the threat of imported counterfeit APIs to U.S. consumers and responding appropriately to that threat.

The growth in international trade over the past few decades has had a substantial impact on the ability of FDA to cope with the volume of regulated products, including APIs. Despite an increase in overall Agency funding in recent years, those increases have been allocated to new initiatives, and the Agency's core operations have not received commensurate increases. Field personnel and resources have been stretched so thin that FDA has been struggling to fulfill many of our program mandates. The increasing number of APIs from overseas makes policing the global drug marketplace to deter or interdict imported substandard drugs a daunting task. We have looked for additional ways in which we can use our own resources wisely, as well as leverage with others to increase our effectiveness.

On June 8, you asked FDA for a plan to improve our ability to detect and interdict imported counterfeit and substandard APIs. We forwarded a preliminary report to you, Mr. Chairman, on August 10, 2000, which outlined the Agency's plans and additional ideas under consideration for better handling imported counterfeit and substandard APIs and finished drugs.

Let me begin by providing the Committee with an update on the five initiatives FDA announced at the June hearing.

1. In February 2000, additional funds were allocated to the Forensic Chemistry Center (FCC) by the Office of Regulatory Affairs for sampling, analytical work and assessments of APIs gathered through targeted inspections of importers.

With these funding increases, the FCC has conducted 20 targeted API inspections, including nine at importers of foreign APIs, ten at domestic finished dosage manufacturers and one at a domestic animal drug manufacturer. The FCC inspectors are now reviewing imported API documents and samples of product, labeling, packaging schemes and certificates of analyses obtained during these inspections. Information derived by these analyses will be used to help determine whether additional follow-up by district office investigators or the Office of Criminal Investigations is needed and to support any enforcement actions that may be warranted. At each of these inspections, the FCC worked with local FDA district drug investigators to detect suspect API shipments through product and records examinations. This activity also provided an opportunity for FCC staff to train field investigators and raise the awareness of District Investigation Branches to the problem of counterfeit API's. Additional hands-on training is planned for investigators in other strategic locations.

2. Make the FCC API database available electronically to all field inspectors by January 2001.

This database currently contains information or “fingerprints” on 330 API's that have been collected and chemically analyzed by FCC. This information is one important tool which FDA can use to more quickly identify whether or not a product is authentic or counterfeit.The technology necessary to make FCC's API database available electronically on a real-time, searchable basis to field import and drug inspectors is being developed, and training for field personnel is being planned. We expect to have this system in place by January 2001.

3. Expand the Philadelphia pilot nationwide by the end of 2000.

A pilot program was begun in the Philadelphia District office in 1997, to evaluate the value of providing drug approval information to import field personnel. The pilot provided import inspectors in the Philadelphia District with access to information contained in the Establishment Evaluation System (EES) database maintained by the Center for Drug Evaluation and Research (CDER). EES tracks information related to the approval process for drug applications. The program allows inspectors to retrieve additional important data in about three to four minutes on any API entry, which increases the probability of confirming authentic sourcing of APIs.

In light of this success, access to the EES system has been expanded to the three FDA Districts handling the vast majority of APIs—New York, New Orleans and San Juan District Offices. Training for these inspectors has been completed and accounts have been established. The system has been up and running for approximately two months, and our inspectors in these districts report that the EES information is very useful in helping to assure that the declared destinations of imported APIs are appropriate. Currently, we are completing plans for the additional technology upgrades and training for field personnel necessary to expand the program to the rest of our districts, which we plan to complete early next year.

4. Put all importers on notice that they are required to provide the name of the foreign manufacturer upon entry into the U.S., and that the entry of their products into the U.S. will be contingent upon it.

The Agency has placed the import industry on notice regarding the existing requirement to provide FDA with accurate data regarding the identity and location of the manufacturer of imported drugs. These requirements were previously made clear to importers and brokers through notices issued on January 29, 1999, and March 24, 2000. However, this requirement was not being fully met. Therefore, on July 20, 2000, the Agency again posted an updated version of its requirements on the Internet with links to and from FDA's import operations pages. On July 28, 2000, a U.S. Customs Service (Customs) Automated Broker Interface (ABI) system administrative message was issued to all filers with a reference to the Internet site containing these requirements and a physical mailing address where a filer may request a hard copy from the Agency. A copy of the July 28, ABI notification was provided in FDA's August 10, letter to the Subcommittee.

Compliance with this requirement is assessed as the Agency carries out routine filer evaluations and is one of the factors considered in providing continued electronic filing privileges on Operational and Administrative System for Import Support (OASIS). Customs has informed FDA that these types of reporting failure may be the basis for Customs civil actions. This information will be useful to the Agency in better defining and identifying the universe of foreign manufacturers shipping to the U.S.

5. Require domestic manufacturers to provide information to FDA when they discover that the bulk materials they receive are substandard, ineffective, or appear not to be from the approved source.

As you know, the Committee proposed this idea to the Agency last year. We stated in June that we agreed this is a promising approach, and FDA is examining what would be required to develop a proposed regulation that would establish this requirement.

Agency Examination of Imported Counterfeit Bulk Drugs

Immediately following the June 8 hearing, FDA established a Counterfeit Drug Working Group (Working Group) which has spent the past three months exploring the full range of issues concerning imported counterfeit and substandard drugs. The Working Group has looked carefully at FDA's import operations and our foreign drug inspection program, and has been developing a plan to better assess the extent of the counterfeit drug problem in the U.S. The Working Group also has been examining ways the Agency can more readily detect these products to better ensure that the public is protected from potentially hazardous drugs.

FDA's Counterfeit Drug Working Group consists of representatives from many Agency components, including: the Office of Criminal Investigations (OCI), the Division of Import Operations and Policy (DIOP), the Office of Enforcement, the Forensic Chemistry Center (FCC), the Division of Federal-State Relations (DFSR), the Division of Information Systems (DIS), and the Division of Emergency and Investigational Operations (DEIO), all of which are components of the Office of Regulatory Affairs (ORA), as well as the Offices of Compliance within the Center for Drug Evaluation and Research (CDER) and the Center for Veterinary Medicine (CVM), and the Office of Chief Counsel (OCC).

While FDA is still in the process of assessing the effectiveness of the regulatory tools, compliance programs, staffing and procedures that already exist within the current statutory construct to monitor imported APIs, the Agency already has implemented a number of program initiatives, including the following actions.

Foreign Registration—FDA has cleared and forwarded to the Office of Management and Budget (OMB) a final rule requiring foreign establishments whose products are imported or offered for import into the U.S. to register with FDA and to identify a U.S. agent. As you know, this requirement was mandated in the Food and Drug Administration Modernization Act of 1997. It will provide for the collection of information needed to establish an accurate Official Establishment Inventory for foreign drug firms.

Information Technology Needs Assessment (IT)—As you know, one of the issues of great concern at the June hearing was the Agency's lack of a well-integrated IT system for the regulation of drug imports. We acknowledged that FDA has been working with several independently developed databases of critical information that need to be integrated. We also understand the Committee's frustration that this problem has not yet been remedied.

In early July, FDA engaged the services of a private IT contractor to assess the Agency's IT needs for drug imports and to propose changes to accomplish the goals described below. The contractor was charged with determining what information FDA import inspectors need to fully assess the admissibility of all FDA regulated commodities. The contractor consulted with import inspectors and compliance officers with expertise in FDA and Customs laws and regulations, good manufacturing practices, and IT import applications. The contractors' report was recently received by the Agency, and we are currently reviewing both the recommendations and the estimated resource requirements.

Cross-training with U.S. Customs Service—In June and July 2000, FDA conducted three Import Enforcement training courses for FDA import personnel including Compliance Officers, Consumer Safety Officers, and Consumer Safety Inspectors. A total of 120 students attended one-week courses representing in total about half of all persons assigned to field import operations. FDA and Customs jointly developed the curriculum and taught the course. The course included training in Strategic Problem Solving (SPS), a Customs training module developed specifically to facilitate the targeting, investigation and prosecution of willful violators. Each course included a facilitated workshop after the pattern of SPS. In each class, students analyzed and provided recommendations for specific imported API counterfeiting fact patterns. These facilitated brainstorming sessions by the field personnel focused on the imported counterfeit API threat and produced numerous ideas for strategies in detecting, preventing, and interdicting counterfeit imported APIs. The Working Group is assessing these proposals for viability.

This training course is being extended to additional field personnel in three sessions that began this week.

Other Cooperative Efforts with Customs—FDA's OCI has a close working relationship with Customs, including a Memorandum of Understanding providing for all OCI agents to be cross-designated as Customs Officers. OCI currently is working a number of on-going investigations with Customs involving unapproved and counterfeit finished human drugs, and adulterated and misbranded medical devices and foods.

OCI and Customs cooperated in a joint operation targeting the Internet sales of unapproved pharmaceuticals by Thailand-based organizations. In cooperation with Thai authorities, Customs arranged for the consolidation and diversion of international mail deliveries of these products to JFK Airport, where FDA personnel were assigned exclusively for review and processing of these entries. In the period February to August 2000, approximately 300 such shipments were reviewed, found to be non-admissible, and returned to Customs for forfeiture.

FDA has also had discussions with Customs' Applied Technology branch and we will be meeting with them this month to explore the use of countermeasure devices to detect counterfeits and track shipments where warranted.

International Collaboration—OCI, through liaison with their international law enforcement counterparts and other regulatory agencies, is a key Agency component in cooperative international efforts aimed at identifying, investigating and prosecuting drug crime. OCI participates in the Permanent Forum on International Pharmaceutical Crime (PFIPC), an international enforcement forum aimed at exchanging information and ideas on combating pharmaceutical crime. PFIPC works in conjunction with a Forensic Group that provides scientific expertise. OCI also maintains contact with their counterparts at the World Health Organization, the World Customs Organization, Interpol, and FDA's counterparts such countries as the United Kingdom, Germany, Spain and Australia. Additionally, the FCC participates in the International Laboratory Forum on Counterfeit Medicines.

Forensic Chemistry Center Initiatives—The FCC and Customs have agreed to explore methods to better leverage their respective resources in the investigation and analysis of suspect counterfeit products. The FCC hosted the first meeting in their forensic laboratory on August 10, 2000, and demonstrated FDA's current forensic capabilities and strategies. The two agencies will explore ways to grant access to analytical data and equipment and cross training in methodologies and emerging forensic techniques. The FCC will interface directly with Customs' laboratories to share information on analytical procedures FDA's forensic experts use to detect unapproved and counterfeit APIs. FDA has placed a high priority on developing with Customs a unified approach for interdicting counterfeit drugs.

Review of Data on Uninspected Firms—In response to a request from Chairman Bliley earlier this year, FDA produced a report based on unverified data from OASIS, which identified listings for approximately 4,600 firms that appeared to be non-inspected foreign drug manufacturers. It should be noted that the OASIS data was input by Customs house brokers at the time that drug entries were filed.

This number of 4,600 "uninspected firms" was the subject of great concern at the June hearing. As explained in our previous testimony, that number was the best estimate we were able to provide on short notice, and was derived by comparing raw data input by import brokers into OASIS with a known list of inspected firms. FDA has reviewed the OASIS data and manually cross-checked it with other information sources to weed out duplicates and incorrect entries and establish a much more accurate list of uninspected foreign drug manufacturers that appear to have exported to the U.S. an API that is normally used to manufacture a finished dosage form which requires an approved application. So far, the review of this data has enabled us to produce a much more reliable list of 242 foreign API manufacturers, in 36 countries, that appear to have exported to the U.S. in 1999, but have not been inspected, according to the EES database. The Agency is developing an import alert for these uninspected foreign drug establishments. The 242 identified firms include forty-six firms in China and Hong Kong and eleven firms in India.

The final phase of the analysis of the OASIS data will be to identify firms FDA has not inspected but which are referenced in approved human and animal drug applications. The human drug firms will be evaluated using a risk-based analysis stratified into one of four tiers, incorporated into FDA's surveillance list, and subsequently scheduled for inspection.

Additional Strategies for Handling Imported Counterfeit, Unapproved Drugs and APIs

Joint Industry/Agency Efforts—Members of the Working Group conferred with the FDA's Field Drug Committee (FDC) on counterfeit API issues. The FDC historically has maintained networks with drug industry personnel and trade associations and has utilized these relationships for furthering the important message of health and safety through consistency in the Good Manufacturing Practice compliance. The FDC will assist in developing avenues through which industry could join forces with the Agency in combating counterfeits in the market place.

Beyond this initial approach through the FDC, the Agency is exploring additional routes for encouraging and receiving intelligence on counterfeit drugs in the world market. Historical experience in prior counterfeit API investigations has demonstrated that foreign API manufacturers whose products are being counterfeited can provide substantial assistance in developing tests for authenticity and intelligence regarding suspected counterfeiting operations. The Agency is aware that intelligence gathering from the trade is a critical element to successfully identifying suspect counterfeits in the market.

Foreign Inspection Component—When faced with the challenge of a steadily increasing volume of needed foreign inspections, coupled with limited resources, a risk-based approach to foreign drug inspection was developed. CDER established a four-tiered approach to prioritizing and performing surveillance inspections of firms that FDA had not previously been able to inspect. At the present resource level, however, FDA is only able to inspect firms in Tier I (Official Action Indicated, or OAI, inspection follow-up) and Tier II (sterile bulks, finished drugs and aerosols). It should be noted that pre-approval inspections are required by the Prescription Drug User Fee Act and most are conducted in accordance with the Act's mandate. Thus, resources are the primary factor limiting the Agency's ability to undertake additional inspections. As I am sure your Committee staff reported back to you after their trip to China and India to observe foreign inspections, foreign inspections are extremely resource intensive—requiring not only highly trained investigative and scientific personnel, but linguistically and culturally competent staff, as well. The time needed to conduct a foreign inspection is also magnified by travel requirements.

The Agency is reassessing these issues and discussing how to best utilize our current resources given current constraints. We hold fast to the belief that there is no substitute for an eyes and hands-on inspection.

Even with these limitations, I would hasten to note that since 1990, the Agency has shifted resources from domestic to foreign programs to increase our presence in the foreign drug manufacturing marketplace, recognizing the shift in global markets. The foreign drug inspection program for the current fiscal year is on track for accomplishing approximately 450 inspections in all foreign drug program areas. This represents more foreign inspections than the Agency has ever completed in a single year. The program continues to be primarily application driven, and the priorities associated with the product approval process do impact our ability to conduct drug surveillance inspections.

For fiscal year (FY) 2001, ORA is projecting approximately 550 foreign inspections associated with its foreign drug work plan in all program areas. The FY 2001 foreign work plan focuses on manufacturers that have not been inspected, as identified through the analysis of OASIS data discussed previously. This includes substantial increases in drug surveillance inspections, which would result in increased coverage of firms in Tiers III and IV. However, to accomplish this increase, a reallocation of existing resources would need to occur by reducing our domestic inspection program.

Import Operations Component—FDA's DIOP is responsible for providing policy guidance to the field relating to import procedures, overseeing the development and operation of the Agency's Import Alert system, and for maintaining the Agency's OASIS system. Customs has identified over 300 designated ports of entry. OASIS data indicates that approximately 175 ports have seen entries of APIs. FDA has a notable presence in over 40 ports. The ports where FDA conducts the bulk of its work represent those through which the vast majority of drugs enter. The Working Group is reviewing DIOP's procedural and system operations and is assessing the Agency's personnel and equipment needs to better monitor U.S. ports of entry.

Security Measures—FDA is engaged in discussions with the Customs' Applied Technology Division, which has considerable experience in tracking shipments within U.S. commerce to verify and document cargo diversion. We will evaluate the currently available technology in terms of levels of surveillance capabilities, cost of equipment and implementation. Additionally, we have asked the IT contractor to explore the possible use of low cost security devices by foreign manufacturers such as chemical taggants in labeling, glue, ink or packaging materials to detect suspect counterfeit drugs. Other possible solutions include radio frequency tags for detection during examinations at ports of entry.

The Agency is considering a wide array of available technology, including encrypted bar code technology in labeling and Certificates of Analysis containing manufacturing information already submitted by the foreign manufacturer through a secure web-based environment.

Mr. Chairman, in June you asked us what additional resources, personnel and funding may be necessary to fully carry out our responsibilities for inspecting foreign drug manufacturers and to increase the surveillance of foreign APIs and finished drugs. The Agency has long recognized that we need additional resources in the area of post-marketing surveillance, which would encompass many of the activities I have just discussed. In just the last two years—FY 1999 and FY 2000—the President's budget included $25.8 million and $39.3 million, respectively, for post-marketing surveillance activities, none of which was funded. The lack of new funding, coupled with an absence of increases for core operations, reduces the number of FTEs available to perform the Agency's critical post-market activities.

At this time, only preliminary estimates have been made of these resource requirements, as the scope of this evaluation needs to encompass both the Agency's domestic and foreign operations, as well as the operations of various FDA Centers. We look forward to providing more specific information on our funding needs relating to personnel and technology in the future, once a complete assessment is made and appropriate review has occurred.

FDA will continue its assessment of the extent of the counterfeit drug problem in the U.S. Over the coming weeks, the strategies outlined above will be further developed and enhanced, and other potential strategies will be considered. While the Agency has already made a good deal of progress, we have much work remaining.

CONCLUSION

Mr. Chairman, I want to assure you that all of us at FDA remain strongly concerned about any possibility that counterfeit or otherwise unsafe drugs may find their way into the American drug supply. We will remain vigilant as we refine and improve the programs and procedures that we use to ensure the availability of safe medications for consumers.

We appreciate the continued interest of the Subcommittee in these important issues. Thank you again for the opportunity to discuss these issues with you, and I will be happy to answer any questions.

Mr. UPTON. Thank you.

Mr. Kelly.

TESTIMONY OF HON. RAYMOND KELLY

Mr. KELLY. Thank you, Mr. Chairman, members of the committee, for the opportunity to testify today. The Customs Service is an agency of almost 20,000 employees stationed at 301 ports of entry and 165 other locations across the country. Many know Customs as the Federal Government's primary drug interdiction agency. One of our greatest challenges is sifting illegal narcotics from the $1 trillion in trade and half a billion travelers we process each year. But the scope of Customs' responsibilities goes well beyond drug interdiction to include money laundering, copyright and trademark infringement, the import and export of weapons of mass destruction, prohibited technologies, forced child labor investigations, child pornography and criminal exploitation of the Internet. We also enforce over 400 regulations for 40 other Federal agencies at our borders, including the laws that prohibits the importation of counterfeit pharmaceutical products.

As we are all aware, legislation is currently pending to allow the U.S. pharmacists and wholesalers to reimport American manufactured, FDA approved drugs from abroad. This morning, I'd like to discuss our concerns about the potential resource implications for our agency.

Customs has experienced a significant spike in investigations and seizures of counterfeit pharmaceuticals over the last few years. One factor in this development is the Internet. We consider the problem serious enough to make it a top priority of Customs' CyberSmuggling Center, which is our new state-of-the-art facility devoted to combating Internet crime.

Part of the mission of the center is to search for foreign companies marketing prohibited or unsafe drugs to U.S. consumers. That information is passed on to our Office of Investigations, which has successfully concluded a number of counterfeit pharmaceutical cases in recent years. Prescription drugs are most commonly sent through U.S. mail. Customs inspectors staff 14 international mail branches at various postal facilities across the United States to deal with these shipments.

To state that finding counterfeit drugs hidden amongst hundreds of millions of parcels is like finding needles in a hay stack would be an understatement. In fact, finding any form of contraband in postal shipments presents a massive challenge.

Our limited resources require a risk management approach, through which we utilize advance intelligence, records of past seizures, and other factors to zero in on packages that present the most significant threat. Customs laboratories also play a critical part in our investigations. Their expertise in analyzing everything from textiles to foreign oil, to food products to determine point of origin and composition is world-renowned.

We maintain fully equipped labs at the following locations: New York, Chicago, Savannah, New Orleans, Los Angeles, San Francisco and San Juan. In addition, we have three mobile labs that deploy at any point along our borders. We are confident in the forensic capability of our labs to find discrepancies in shipments of bulk and finished pharmaceuticals. But where we do require assistance specifically from the Food and Drug Administration is in determining effective national standards for interdiction of these products. These standards will be critical especially in light of the pending legislation.

To that end, Customs initiated a request to the FDA last January for further guidance on detaining suspect pharmaceuticals. In addition, we formed a joint task force with FDA in August to examine shipments of online drug purchases. The task force's work will include the set-up of a pilot examination program in Los Angeles beginning on October 23.

We've asked the FDA to develop interim guidelines to cover the illegal shipments we are taking in now for both online and bulk pharmaceuticals. Customs has already begun examining shipments of pharmaceuticals as part of Operation Safeguard, our ongoing enforcement program with FDA. The first phase began September 25 at the Customs mail facilities in Oakland, California and here in Washington at Dulles Airport. So far we've detained 200 shipments. To give the members an example, our seizures included a 3000-tablet shipment of Prozac with an expiration date of 1980.

In addition, our Office of Investigations maintains a close relationship with its FDA counterpart. We have a memorandum of understanding, as the Commissioner mentioned, in place with the FDA at our field locations that cross-designates their special agents as Customs officers. Customs has also provided training to FDA officials on import enforcement. We will continue do so throughout the course of the next fiscal year.

Mr. Chairman, our biggest concern in the face of new legislation is obtaining adequate resources to enforce it. From an overall Customs perspective, a spiraling volume of goods at our borders has put immense pressure on our ability to facilitate international trade while enforcing our Nation's laws. We've taken many steps to address anticipated challenges, including refinement of our targeting approach and development of a Resource Allocation Model to project future staffing needs across the country. Though this study has not been finally approved by OMB and the Treasury Department, once it is it will allow flexibility in building in new resource needs like the one we are discussing today.

We just received the resource package FDA has developed and we are reviewing it right now. That analysis and the development of the national standards I referred to will help us greatly in determining our own requirements.

Customs encounters many travelers in our borders returning from trips expressly for the purpose of purchasing drugs. We are very familiar with the lengths to which our citizens will go to obtain savings on health costs. I should note that for the public's information implementation of the Medicine Equity and Safety Act would not affect individuals who travel across our northern and southern borders to obtain prescription drugs. They would continue to be subject to existing laws that apply to such purchases. Nor would online purchases by consumers be impacted. They too would be regulated according to current guidelines.

Mr. Chairman, I want to thank you and the members of the committee for considering the Customs Service in your discussions of the importation of pharmaceuticals. This is an issue that speaks directly to our mission. We will continue to make every effort possible to work with the Congress and our fellow inspection agencies to address the health and safety concerns of the American people.

Thank you.

[The prepared statement of Hon. Raymond Kelly follows:]

PREPARED STATEMENT OF HON. RAYMOND KELLY, COMMISSIONER, U.S. CUSTOMS SERVICE

Mr. Chairman, members of the committee, thank you for this opportunity to testify.

As Commissioner of U.S. Customs, I oversee an agency of 20,000 employees stationed at 301 ports of entry across the country. Many know Customs as the federal government's leading drug interdiction agency. One of our greatest challenges is sifting illegal narcotics from the 1 trillion dollars in trade and half a billion travelers we process each year.

But the scope of Customs responsibilities goes well beyond drug interdiction to include: money laundering; copyright and trademark infringement; the import and export of weapons of mass destruction and prohibited technologies; forced child labor investigations; child pornography; and criminal exploitation of the Internet.

We also enforce over 400 regulations for 40 other federal agencies at our borders, including the laws that prohibit the importation of counterfeit pharmaceutical products, the topic I am here to discuss with you today.

As you are all aware, legislation is currently pending to allow U.S. pharmacists and wholesalers to re-import American manufactured, FDA approved drugs from abroad. This is an effort to lower prescription drug costs for consumers. This morning I would like to discuss the bill and its impact on our agency.

Customs has experienced a significant spike in its investigations and seizures of counterfeit pharmaceuticals over the last few years. One factor in this development is the Internet. We consider the problem serious enough to make it a top priority of Customs' Cybersmuggling Center, our new, state-of-the-art facility devoted to combating Internet crime.

Part of the mission of the Center is to search for foreign companies marketing prohibited or unsafe drugs to U.S. consumers. That information is passed on to our Office of Investigations, which has successfully concluded a number of counterfeit pharmaceutical cases in recent years.

Prescription drugs are most commonly sent through U.S. mail. Customs Inspectors staff fourteen international mail branches at various postal facilities across the United States to deal with these shipments.

To state that finding counterfeit drugs hidden amongst hundreds of millions of parcels is like finding needles in a haystack would be an understatement. In fact, finding any form of contraband in postal shipments presents a massive challenge. Our limited resources require a risk management approach, through which we utilize advance intelligence, records of past seizures, and other factors to zero in on packages that present the most significant threat.

Customs laboratories also play a critical part in our investigations. Their expertise in analyzing everything from textiles, to foreign oil, to food products to determine point of origin and composition is world-renowned. We maintain fully-equipped labs at the following locations: New York; Chicago; Savannah; New Orleans; Los Angeles; San Francisco and San Juan. In addition, we have three mobile labs to deploy at any point along our borders.

We're confident in the forensic capability of our labs to find discrepancies in shipments of bulk and finished pharmaceuticals. But where we do require assistance, specifically from the Food and Drug Administration, is in determining effective national standards for interdiction of these products.

These standards will be critical especially in light of the pending legislation. To that end, Customs initiated a request to the FDA last January for further guidance on detaining suspect pharmaceuticals. In addition, we formed a joint task force in August to examine shipments of on-line drug purchases. The task force's work will include the set-up of a pilot examination program in Los Angeles beginning on October 23rd.

In the meantime, I've urged the FDA to develop interim guidelines to cover the illegal shipments we're taking in now. Customs has already begun examining shipments of pharmaceuticals as part of "Operation Safeguard." The first phase of this operation began September 25th, at the Customs mail facilities in Oakland, California and here in Washington, at Dulles Airport. So far, we've detained 200 shipments. To give the members an example, our seizures included a three thousand-tab shipment of Prozac with an expiration date of 1980 on it.

In addition, our Office of Investigations maintains a close relationship with its FDA counterpart. We have a Memorandum of Understanding in place with the FDA at our field locations that cross-designates their special agents as Customs officers. Customs has also provided training to FDA officials on import enforcement. We'll continue to do so throughout the course of the next fiscal year.

Mr. Chairman, our biggest challenge in the face of the new legislation is keeping pace with the spiraling volume of goods at our borders while also enforcing our nation's laws. We've taken many steps to address anticipated challenges, including refinement of our targeting approach and development of a strong resource allocation plan.

We recently received the resource projections FDA has developed for its own needs under the new legislation and we're reviewing it now. That analysis, and the development of the national standards I just referred to, will help us greatly in determining our own requirements.

I should note for the public's information that implementation of the Medicine Equity and Safety Act would not affect individuals who travel across our northern and southern borders to obtain prescription drugs. They would continue to be subject to existing laws that apply to such purchases. Nor would on-line purchases by consumers be impacted. They too would be regulated according to current guidelines.

Mr. Chairman, I want to thank you and the members of the Committee for considering the Customs Service in your discussions of the importation of bulk pharmaceuticals. This is an issue that speaks directly to our mission. We will continue to make every effort possible to work with the Congress and our fellow inspection agencies to address the health and safety concerns of the American people.

I'd be happy to take any questions you have.

Mr. UPTON. Thank you.

Ms. Maher.

TESTIMONY OF PATRICIA L. MAHER

Ms. MAHER. Mr. Chairman and members of the committee, good morning. My name is Patricia Maher. I am a Deputy Assistant Attorney General in the Civil Division of the Department of justice. In that capacity one of my responsibilities is to oversee the Office of Consumer Litigation, the Civil Division's office that handles civil and criminal cases brought under a number of Federal consumer protection statutes, including the Federal Food, Drug and Cosmetic Act.

This morning I will speak to you about our experience prosecuting traffickers of counterfeit pharmaceutical products that are manufactured outside of the United States. I will also offer some ideas regarding additional tools that would be helpful to combat this problem.

Prosecutions of the type I will be discussing are both important and difficult. They are important because the targets in these cases introduce drugs of unknown safety and efficacy into the United States. Successful prosecutions signal to traffickers around the world that tainting the drug supply of the United States will not be tolerated. But these cases are difficult because much of the evidence of unlawful activity is located overseas and thus is more difficult to obtain than evidence located within our borders.

While we have been successful in overcoming these hurdles and obtaining convictions, we need your help to eliminate obstacles that slow investigations and create questions regarding the applicability of the act to the behavior that is at issue in these cases.

The Food, Drug and Cosmetic Act defines a counterfeit drug to include a drug which without authorization bears an identifying mark of another drug manufacturer that did not manufacture the drug. Under the act the term "drug" includes both finished drug products and components of drug products that are referred to as bulk pharmaceuticals or active pharmaceutical ingredients.

In the pharmaceutical industry the term "counterfeit drug" is generally used to refer to a compound that is not made by the authorized manufacturer but is presented to the consumer as if it were.

Counterfeit drugs pose a number of potential public health issues. They may contain a less potent ingredient than claimed, ingredients other than those listed or no active ingredient at all, which makes them less effective and possibly toxic to unknowing consumers. The World Health Organization has estimated that as much of 10 percent of the world's supply of branded medicines are counterfeit, with the level rising to 50 percent in some developing countries.

Prosecutions are necessary to reach counterfeit operations that fall outside the regulatory system where the drugs are going to be introduced into the United States. Prosecutions for importation of counterfeit products have relied primarily on evidence gathered domestically, whether the defendants are citizens of this country or foreign nationals.

In my written testimony I provided two examples of successful prosecutions of drug counterfeiters. One involved a ring of traffickers importing millions of counterfeit birth control pills from Spain and Guatemala. The other case involved a company called Flavine International, which imported counterfeit antibiotics from China.

There are unique challenges when groups acting outside the United States import counterfeit pharmaceutical products. Even when extraterritorial jurisdiction exists over crimes committed abroad, principles of sovereignty limit what measures we can take unilaterally to investigate and prosecute such crimes. FDA currently has the authority to conduct inspections abroad. Letters rogatory are the customary method of obtaining assistance from abroad in the absence of a treaty or executive agreement.

In order to improve our ability to investigate and pursue evidence and defendants abroad, the Department has supported extradition treaties to obtain the return of defendants and mutual legal assistance requests to obtain documents, witness testimony, or other evidence. Of course, even when extradition treaties and mutual legal assistance procedures are in plates with the foreign jurisdiction, they may not always ensure that we will be able to obtain all of the international law enforcement cooperation we would like in every case.

As I have explained in greater detail in my written testimony, extradition treaties do not ensure that defendants will be returned to the United States for prosecution if they are from countries that will not extradite their own citizens, or the underlying conduct is not a crime in the requested State.

Moreover, while we may seek to obtain the statements or deposition testimony of foreign witnesses unwilling to come to the United States through the traditional letters rogatory method or through our increasing number of mutual legal assistance treaties, in the best of circumstances this can be a time consuming process. In the worst of circumstances, legal privileges or other foreign law requirements may completely frustrate our efforts.

Despite their limitations, however, modern international extradition treaties and MLATs remain among the more effective mechanisms available for obtaining the international cooperation we need. We ask that Congress continue to support our efforts to expand the network of such agreements. Certain measures could be taken that would make clear that foreign manufacturers or distributors of pharmaceuticals in the United States are subject to the same obligations and protections that apply to domestic companies. These proposals would also aid in the prosecution of producers or traffickers of counterfeit pharmaceuticals who know that their products will be used in the United States.

First, we believe that foreign countries should be encouraged to cooperate with the United States and, where appropriate, to prosecute manufacturers and distributors of counterfeit drugs in their own courts. We ask Congress to review carefully proposals that might deny or restrict FDA's authority to inspect foreign establishments. Other possible measures include amending the Food, Drug and Cosmetic Act to make explicit what is now implicit, that foreign companies and individuals who manufacture and distribute drugs and drug components for use in the United States are subject to the act, making cooperation by foreign firms a condition of FDA approval of drug applications by those firms so that the approval under the act would be conditioned on the manufacturer's agreement to make documents and witnesses available in criminal investigations in the United States.

Finally, Congress could require foreign exporters of drug products to provide original certificates of analysis establishing the integrity and authenticity of the drugs or drug components that would have to be filled out by each manufacturer involved in the production of the drug product shipped.

The Department recommends these actions and policies to provide additional tools for the detection and prosecution of those who traffic in counterfeit pharmaceutical products. We will work with FDA, Customs, Congress and industry to implement measures of this type to aid prosecutions in this area. Where counterfeiting activity is uncovered we are committed to prosecuting such cases.

Thank you. I would be happy to answer any questions.

[The prepared statement of Patricia L. Maher follows:]

PREPARED STATEMENT OF PATRICIA L. MAHER, DEPUTY ASSISTANT ATTORNEY GENERAL, CIVIL DIVISION, U.S. DEPARTMENT OF JUSTICE

Mr. Chairman and Members of the Subcommittee: Good morning. My name is Patricia L. Maher. I am a Deputy Assistant Attorney General in the Civil Division of the Department of Justice. In that capacity, one of my responsibilities is to oversee the Office of Consumer Litigation (OCL)—the Civil Division's office that handles civil and criminal cases brought under a number of federal consumer protection statutes including the Federal Food, Drug, and Cosmetic Act (FDCA). This morning, at your invitation, I will speak to you about our experience prosecuting traffickers of counterfeit pharmaceutical products that are manufactured outside of the United States. At your request, I will also offer some ideas regarding additional tools that would be helpful to combat this problem.

Prosecutions of the type I will be discussing are both important and difficult. They are important because the targets in these cases introduce drugs of unknown safety and efficacy into the United States. Successful prosecutions signal to traffickers the world over that tainting the drug supply in the United States will not be tolerated. The cases are difficult because much of the evidence of unlawful activity is located overseas, and thus is more difficult to obtain than evidence located within our borders. While we have been successful in overcoming these hurdles and obtaining convictions, we need your help to eliminate obstacles that slow investigations and create questions regarding the applicability of the FDCA to the behavior that is at issue in these cases. In that connection, we will work and consult with FDA regarding needed changes in the Food, Drug and Cosmetic Act, such as those described in this testimony.

As evidence of U.S. law enforcement's commitment to combat the threat posed by counterfeit pharmaceuticals, the Department of Justice, FBI, and Customs Service hosted last month the first meeting of law enforcement experts of the G-8 countries to address intellectual property crimes. Under the auspices of the Senior Law Enforcement Experts on Transnational Organized Crime (Lyon Group), representatives from all G-8 countries discussed mechanisms for improved cooperation and information-sharing in responding to a variety of intellectual property crimes, including trafficking in counterfeit pharmaceuticals.

I. THE DANGER POSED BY THE IMPORTATION OF COUNTERFEIT PHARMACEUTICAL PRODUCTS

The FDCA defines a counterfeit drug to include a drug which, without authorization, bears an identifying mark of another drug manufacturer that did not manufacture the drug. (21 U.S.C. § 321(g)(2).) Under the FDCA, the term "drug" includes both finished drug products and components of drug products that are referred to as "bulk" pharmaceuticals or active pharmaceutical ingredients. In the pharmaceutical industry, the term "counterfeit drug" is generally used to refer to a compound that is not made by the authorized manufacturer, but is presented to the consumer as if it were.

There are also drug products that are manufactured in whole or in part by unauthorized factories or facilities, and then shipped with the complicity of the authorized manufacturer under its name and trademark. These drugs may not technically fit the legal definition of "counterfeit drug" if the authorized manufacturer has approved the use of its own trademark and the like. Nonetheless, these drugs involve the marketing of a product where the identity of the true manufacturer is misrepresented to, or withheld from, consumers and the Food and Drug Administration (FDA) and the drug is misbranded under the FDCA. As a consequence, some or all of the process of manufacturing the drug could fall outside the supervision of the FDA and could render the drug adulterated or misbranded. Because such drugs also involve a false representation about their true place of manufacture, they can be referred to as misbranded or adulterated.

Counterfeit drugs pose a number of potential public health issues. The World Health Organization (WHO) has found that the majority of counterfeit drugs reported to the organization contain a less potent active ingredient than claimed, ingredients other than those listed, or no active ingredient at all, which makes them less effective and possibly toxic to unknowing consumers. WHO has estimated that as much as ten percent of the world's supply of branded medicines are counterfeit, with the level rising to fifty percent in some developing countries.

Even where the product in question contains the represented amount of the drug's active ingredient, it can pose hazards. The effectiveness of drugs depend on a long chain of factors that include measures in quality control, distribution, and inventory control. The FDCA requires that all drugs in this country be manufactured under pursuant to the good manufacturing practice regulations to ensure the consistent safety and efficacy of the drug product.

The scope of the problem in the United States should be substantially less than it is in the rest of the world. Several legal provisions help to assure that imported products comply with legal requirements. Drug companies in this country are required to sample and test bulk drugs, whether obtained domestically or internationally, that will be used in finished drug products, as well as to examine the labeling of any such shipments. (*See* 21 C.F.R. § 211.84.) These measures help to assure that bogus drugs will be detected if they are sold to a legitimate finished dosage manufacturer in the United States.

Misbranded versions of a number of drug products have appeared in the United States, nevertheless. The potential for an increase in such traffic exists because of the increasingly global nature of the pharmaceutical business. Moreover, the ease with which counterfeit products can be distributed by "pharmacies" that appear on the Internet makes this an issue that affects consumers directly.

II. OBTAINING ASSISTANCE FROM FOREIGN GOVERNMENTS AND PROSECUTING CONDUCT OCCURRING OUTSIDE THE UNITED STATES

A. The Need for Credible Criminal Deterrence

Underlying the FDCA's statutory scheme to protect the public health is the requirement that regulated businesses deal truthfully with the FDA. Most businesses do so. Because the FDA and our national scheme for drug safety rely on information supplied by regulated businesses, it is necessary to take strong action against those that provide false information to the FDA. The means for punishing fraudulent conduct are contained in the criminal provisions of the FDCA. The general provisions of the criminal code that prohibit false statements to government agencies also apply to false statements made regarding pharmaceuticals. The importation of counterfeit drugs very often involves fraud on the FDA and purchasing customers about the true source or nature of the drug. This is classic felony conduct under the FDCA.

Counterfeiting products can yield huge profits and is a longstanding practice in some areas around the globe. Furthermore, the incentive to mislead FDA about the source of a product's manufacture may exist even where the product contains the same active ingredients. The market for pharmaceutical drugs in the United States is substantial, and it is only open to drug products that are properly approved. Because proper approval is rigorous and demanding, there is a strong economic incentive to mislead FDA to obtain market access without the full expense of proper testing and evaluation. Similarly, there is a strong economic incentive to get FDA approval before other companies, and to maximize the output of a drug before other companies obtain approval for a competing version of the drug. One way for a drug manufacturer to maximize output within such a window is to obtain drug components or drug products from other, non-approved, facilities without notifying customers or the FDA.

Prosecutions are necessary to reach counterfeit operations that fall outside the regulatory system, where the drugs are going to be introduced into the United States. The operations of some drug counterfeiters are much the same as those of the narcotics trade, crossing many borders and involving the use of clandestine facilities. In such circumstances, FDA's regulatory measures and controls are less likely to uncover the activity and impose a punishment sufficient to act as a deterrent.

B. Previous Experience in Obtaining Evidence Abroad in Prosecutions Involving the Importation of Counterfeit Pharmaceutical Products

Prosecutions for importation of counterfeit products have relied primarily on evidence gathered domestically, whether the defendants are citizens of this country or foreign nationals. For example, the 1987 prosecution of a ring importing millions of counterfeit birth control pills from Spain and Guatemala was based entirely on evidence gathered in the United States. Similarly, the *Flavine International* case, which involved a group importing counterfeit antibiotics from China, also was based primarily on evidence gathered within the United States. I will elaborate on these examples of our experience prosecuting importation of counterfeit pharmaceuticals.

1. Example: the prosecution of importers of counterfeit birth control pills—In the mid 1980s, approximately two million counterfeit birth control pills were imported as part of a drug diversion scheme. A large number of the pills contained subpotent estrogen or no estrogen. The case began when a group of traffickers acting both inside and outside the United States began importing, repacking, and distributing counterfeit birth control pills that had been manufactured in Barcelona, Spain. The tablets were similar in appearance and composition to genuine Ovulen-21 tablets made by Searle. These pills were shipped from Spain to intermediary countries, and then smuggled into the United States and sold. The proceeds of the sales, including over $200,000 profits, were deposited in a Panamanian bank account.

Having made a substantial profit on the counterfeit Ovulen, the defendants next solicited a small company in Guatemala to make counterfeit pills that again would appear to be genuine, but in this case would have no active ingredient at all. The Guatemalan company shipped 12,000 cycles of the pill to the United States in August 1984. FDA learned of the counterfeit birth control pills in October 1984. The government gathered evidence from witnesses in the United States, including some of the traffickers who decided to cooperate.

An Indictment filed in the Southern District of Florida in February 1987 charged six defendants who resided in the United States. All defendants were convicted either after pleading guilty or going to trial. The defendants were sentenced to terms of imprisonment of up to twenty-four years.

2. Example: the prosecution of counterfeit antibiotics from China—The prosecution of a New Jersey corporation, Flavine International, Inc. (Flavine), its owner who was a German national, and other company managers was based on the substitution of an unapproved foreign product for an FDA-approved foreign product. The investigation, which was conducted by the United States Customs Service and the FDA, revealed that on numerous occasions from August 1985 through November 1991, the defendants solicited and received orders from drug manufacturers in the United States for bulk antibiotics that are FDA-approved for use in the United States. The drugs included oxytetracycline, gentamicin sulfate, and sulfamethazine. The drugs were sold for use in animal and human drugs. To fill these orders, defendants bought drugs from an unapproved overseas manufacturer, falsely declaring their origin.

Once the unapproved products arrived in the United States, the defendants, when necessary, had the product repacked in new containers that more closely resembled those of the approved manufacturer. Defendants removed labels from containers and affixed fraudulent labels to containers in order to falsify the origin and manufacturer of the drug product. They also replaced the manufacturers' certificates of analysis with fraudulent certificates of analysis that falsely claimed that the drugs were made by an approved manufacturer. These acts were performed without the authorization of the approved manufacturer whose name was used.

In April 1997, Flavine was fined a total of $925,000, and its owner was sentenced to two years in prison and fined a total of $75,000 for illegally importing counterfeit pharmaceuticals from China and laundering money in a kickback scheme.

C. Obtaining and Developing Evidence of Conduct Abroad

There are unique challenges when groups acting outside the United States import counterfeit pharmaceutical products. Even in those circumstances in which extraterritorial jurisdiction exists over crimes committed abroad, principles of sovereignty limit what measures we can take unilaterally to investigate and prosecute such crimes. In some cases, law enforcement agencies in the United States, such as the Customs Service and the Food and Drug Administration (FDA), may make requests of law enforcement agencies abroad informally or through Interpol. State ethics rules, however, may effectively prevent contact with employees of corporations under investigation through such informal contacts. This occurs because federal law now requires Department of Justice attorneys to comply with state ethics rules. Such rules (*see* Model Rule 4.2) often can effectively bar contacts with employees of corporations unless corporate counsel authorizes the communication. FDA also currently has the authority to conduct inspections abroad. (*See* 21 U.S.C. § 374.) Letters rogatory are the customary method of obtaining assistance from abroad in the absence of a treaty or executive agreement. (*See* 28 U.S.C. § 1781.)

In order to improve our ability to investigate and pursue evidence and defendants abroad, the Department has supported extradition treaties to obtain the return of defendants, and mutual legal assistance requests to obtain documents, witness testimony, or other evidence. Of course even when extradition treaties and mutual legal assistance procedures are in place with a foreign jurisdiction, they may not always ensure that we will be able to obtain all of the international law enforcement cooperation we would like in every case. For example, even our most modern extradition treaties require that an offense for which extradition is sought be a crime in both the requesting and the requested state (the "dual criminality" principle). Thus, to the extent that some foreign countries have to date not criminalized the counterfeiting of pharmaceuticals, the extradition of persons from such countries wanted for prosecution in the United States may not be possible. In addition, some older extradition treaties do not clearly cover offenses that are perpetrated in a foreign country yet take effect in the United States; and despite our continuing efforts, some countries still refuse to extradite their own nationals.

Moreover, while we may seek to obtain the statements or deposition testimony of foreign witnesses unwilling to come to the United States (through the traditional "letters rogatory" method, or through our increasing number of mutual legal assistance treaties (MLATs)), in the best of circumstances this can be a time consuming process. In the worst of circumstances, legal privileges or other foreign law requirements may completely frustrate our efforts.

Despite their limitations, however, modern international extradition treaties and MLATs remain among the more effective mechanisms available for obtaining the international cooperation we need. We ask that Congress continue to support our efforts to expand the network of such agreements.

D. Jurisdictional Questions

Among the considerations in obtaining evidence and pursuing prosecutions in these cases is the extraterritorial application of the FDCA. Congress has the power to address the problem of counterfeit pharmaceutical imports even when it involves conduct occurring overseas that has an impact in the United States. Amending the FDCA to make the extraterritorial application of the FDCA to persons affecting the United States by their actions abroad explicit instead of implicit would aid the investigation of criminal cases in these situations. Such an approach would be consistent with the international law principles that United States courts apply. Indeed, international law principles have expanded to permit jurisdiction upon a mere showing of intent to produce effects in this country, without requiring proof of an overt act or actual effect within the United States. Although cases involving intended but unrealized effects are rare, international law does not preclude jurisdiction in such instances, subject to the principle of reasonableness. Thus, we believe that foreign manufacturers of pharmaceutical bulk materials who know that the product will be used in the United States are subject to the jurisdiction of the United States and the FDCA.

The FDCA prohibits the introduction into interstate commerce of adulterated or misbranded drugs (21 U.S.C. § 331(a)), and defines "interstate commerce" to include commerce between "any State or Territory and any place outside thereof," (21 U.S.C. § 321(b)). In construing Title VII of the Civil Rights Act of 1964, which had a similarly broad statement of application, a divided Supreme Court found that such language falls short of demonstrating the affirmative legislative intent required to extend the protections of American law beyond our territorial borders. That decision, *EEOC v. Arabian American Oil Co.,* ultimately was superseded by statute. In this opinion, however, the Supreme Court specifically named the FDCA as a statute with "boilerplate" language that could be insufficient to convey a legislative intent to apply extraterritorially. (*See Arabian American Oil Co.,* 499 U.S. at 251.) The Controlled Substances Act, by contrast, contains explicit language creating jurisdiction in the United States for manufacturing or distributing drugs abroad, where the intent is to introduce unlawful drugs into the United States. (*See* 21 U.S.C. § 959.)

III. PROPOSALS FOR IMPROVING THE PROSPECTS FOR CRIMINAL PROSECUTIONS INVOLVING COUNTERFEIT PHARMACEUTICAL PRODUCTS

We believe that prosecutions of counterfeit drug producers and traffickers would be greatly aided by amending the FDCA to make explicit what is now implicit—that foreign companies and individuals who manufacture or distribute drugs and drug components for use in the United States are subject to the FDCA. The application of such a law, however, will necessarily be limited by due process considerations.

Second, we would ask that Congress review carefully treaties that might deny FDA full authority to inspect foreign establishments. The Department supports FDA retaining its current legal authority to inspect foreign establishments even where FDA has entered into agreements with foreign regulatory agencies to have those agencies conduct the inspections. In addition, the approval to manufacture and/or distribute drugs and drug components in the United States could be conditioned on the manufacturer's or distributor's agreement to make documents and witnesses available in criminal investigations in the United States. FDA currently has the right to inspect drug manufacturers (*see* 21 U.S.C. § 374), but this section does not explicitly provide the FDA authority to secure interviews with witnesses or any method by which the production of documents can be compelled independent of an inspection. As previously mentioned, it is difficult to obtain testimony of witnesses regarding conduct occurring outside the United States.

Clarifying FDA authority as outlined above would make foreign establishments subject to the same obligations, privileges, rights, and protections that apply to domestic firms. Currently, during FDA's regulatory investigations of foreign firms, only certain production records and personnel are made available to inspectors. (*See* 21 U.S.C. § 374.) An explicit requirement that a company must provide such cooperation could authorize FDA to withhold or deny approval of drug applications, and to withdraw a firm's existing approved applications, if FDA finds that the foreign firm is not cooperating in an investigation. This would be analogous to FDA's existing authority to refuse the new drug application of an applicant that has submitted false data to the agency. (*See* Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities; Final Policy, 56 Fed. Reg. 46191 (1991).) Foreign businesses choosing to market pharmaceutical products in this country should not be able to gain better treatment than domestic firms because of their location outside of the country.

Third, the Department requests that the Congress consider legislation requiring foreign exporters of drug products to provide original certificates of analysis establishing the integrity and authenticity of the drugs or drug components filled out by each manufacturer involved in the production of the shipment of a drug product. Such a change would depart only slightly from current practice. The FDCA provides that a drug is misbranded if its labeling is false or misleading. (*See* 21 U.S.C. § 352(a).) In addition, the regulations establish that the appearance of a name on a drug product label, without qualification, is a representation that the company is the sole manufacturer. (*See* 21 C.F.R. § 201.1(h)(2).) If a manufacturer performs more than half of the operations, it meets its obligations if it states that certain manufacturing operations have been performed by other firms. (*See id.* at § 201.1(c)(1).) A simple means of ensuring authenticity of drug components could be accomplished by a minimal expansion of these requirements to apply to foreign firms.

Finally, we believe that foreign countries should be encouraged to cooperate with the United States and, where appropriate, to prosecute manufacturers and distributors of counterfeit drugs in their own courts. Where foreign nations can prosecute such conduct, it is in the United States' interest to help such prosecutions go forward. Increased cooperation with foreign authorities could also facilitate the detection of such criminal activity.

The Department recommends these actions and policies to provide additional tools for the detection and prosecution of those who traffic in counterfeit pharmaceutical products. Where such activity is uncovered, we are committed to prosecuting such cases.

Mr. Chairman and members of the Subcommittee, thank you for the opportunity to testify before the Subcommittee. I look forward to answering your questions.

Mr. UPTON. Thank you very much. The Chair, in talking to a number of members on both sides of the aisle, had a request that we go to a 10-minute question period instead of the normal 5. I need to make that formally. Does anyone have an objection to do that? If not, that will be the course of the day, and I will first recognize the chairman of the full committee, Mr. Bliley, for 10 minutes.

Chairman BLILEY. I thank you, Mr. Chairman.

Dr. Henney, as you know, the language approved in the Senate-passed agricultural appropriations bill required that regulations provide the Secretary of HHS a reasonable assurance that imported drugs are safe and effective. But drugs currently manufactured for consumption by Americans must meet rigorous standards for safety and efficacy as put forth in section 505 of the Food, Drug, and Cosmetic Act. What is the administration's position regarding the standards which should be applied to drugs that are reimported or imported from foreign manufacturing facilities into the U.S.?

Would you agree with me that reimported or imported drugs should be required to meet the same standards as drugs manufactured for U.S. consumption?

Ms. HENNEY. Mr. Chairman, I believe that both the administration, the Secretary as well, as Mr. Lew in his communications with the committee has made clear their position with respect to this bill, there is very strong opposition to the amendments as proposed by Mr. Crowley and Coburn. However, the discussion I believe is focused, as you know, particularly on the amendments offered by Mr. Jeffords to our Senate appropriations bill.

I think there is one thing that we have stressed very strongly, and that is the general support for the framework or paradigm that might be put in place, but it will be totally unworkable unless the FDA is funded to support the initiative in question, and certainly we would expect that the kind of affirmation of the system of safety would at least be equivalent to what we have now.

Chairman BLILEY. I think I got it straight. It was a nice long statement, but are you saying that then you agree with me that it should meet the same standard of safety and efficacy as drugs manufactured in the United States?

Ms. HENNEY. I believe what I am saying, Mr. Chairman, is that there should be no lowering of the safety net that now protects the American citizens.

Chairman BLILEY. Well, do you believe the Senate language that only requires a reasonable assurance of safety and efficacy meets that standard?

Ms. HENNEY. Mr. Chairman, I don't believe that I have undertaken a thorough analysis from the legal perspective of what that reasonableness standard might mean. I think it is very clear that all of us concerned with the kinds of medications that people take in this country want them to meet at least the standard of safety that we now have in place for our citizens.

Chairman BLILEY. In other words, they should comply with section 505, right?

Ms. HENNEY. Mr. Chairman, I believe that the safety standards of this country with respect to prescription drugs have always been to be safe and effective for their intended use. I think that that standard should apply no matter where the drug comes from.

Chairman BLILEY. Thank you, Mr. Chairman. I've got to leave for another meeting. I will try to get back.

Mr. BURR [presiding]. I thank the chairman. As we play musical chairs, the chairman would recognize the gentleman from Michigan.

Mr. DINGELL. Mr. Chairman, I thank you. Commissioner and Mr. Kelly, what would you need in the way of resources to properly enforce our current laws at the ports of entry? That is an answer you are not prepared to give this morning. So will you please submit it for the record.

Mr. KELLY. Yes, sir.

[The following was received for the record:]

The Food and Drug Administration (FDA or the Agency) is not prepared to articulate a specific resource need at this time. However, as you know, the Agency acknowledges that it lacks sufficient resources to conduct comprehensive coverage at all U.S. borders.

In response to the Committee's questions posed on June 8, 2000, FDA began re-evaluating its use of the limited resources available for import operations by developing a resource model. FDA is re-evaluating its current operations to determine where procedures should be updated and revised to better address dynamic industry shifts and make better use of current resources. Any useful resource model would depend upon this current operation evaluation which is still on going. Nevertheless, the ratio comparisons described below may be useful in created a base line for resource discussions.

As discussed more fully later, we have implemented an import alert that focuses on certain active pharmaceutical ingredients (APIs) that do not appear to have been manufactured at facilities identified as an FDA approved sources in an application. We will need to evaluate the results of the Import Alert, including the results of inspections at the dosage form manufacturers and investigations of all intermediaries involved with the product, in order to more fully understand the magnitude of the actual and potential importation of unapproved APIs. The results of these investigations will provide important information relevant to determining additional resources requirements.

Mr. DINGELL. Second of all, Mr. Kelly, does your agency enforce Food and Drug laws at the port of entry?

Mr. KELLY. Yes, sir, we do, along, as I said with my prepared remarks, with the rules and regulations, the laws of 40 agencies.

Mr. DINGELL. Now, Dr. Henney, at how many of the ports of entry do you have Food and Drug people to approve admission of drugs and prescription pharmaceuticals?

Ms. HENNEY. Well, Mr. Dingell, I think that while we have——

Mr. DINGELL. Just how many, please? I have limited time.

Ms. HENNEY. I don't know a precise number.

Mr. DINGELL. Would you please submit that for the record?

Ms. HENNEY. I would be pleased to submit it for the record.

[The following was received for the record:]

The U.S. Customs Service (Customs) recognizes approximately 301 "ports of entry." FDA maintains district offices or resident posts in the metropolitan areas adjacent to 94 of these ports, although only 37 offices or resident posts include staff involved with import operations. The other 57 offices or resident posts are for the most part small resident posts whose responsibilities are limited to domestic products.

FDA receives notification of the entry of FDA-regulated products, either through Customs' ACS system, or through paper entry documents collected by Customs at all ports of entry, even those at which FDA staff are not always present. Even if the product is "conditionally" released by Customs without FDA examination, it is not released into commerce until FDA reviews the entry documentation. If FDA decides to collect a sample or otherwise examine the product after the product has left the port area, Customs can (under the terms of the importer's entry bond) order the product redelivered for FDA examination.

Mr. DINGELL. Now you are behind, Dr. Henney, in your foreign inspections. You have some, I heard the figure, 4600 plants not inspected. You've given us the number of 272, is that correct? Is that a hard number or not?

Ms. HENNEY. 242. To the best of our ability, yes, that is a firm——

Mr. DINGELL. And the number does grow. How long will it take you to complete the inspections of those 242? How much will each of the inspections cost you?

Ms. HENNEY. I will be glad to submit that figure for the record. I don't have it off the top——

[The following was received for the record:]

It is expected that very few, if any, of the 242 firms FDA has identified will require a physical inspection. The goal in identifying these firms was to identify any firms that appear to be improperly shipping APIs into the U.S. and to determine, based on additional information, whether any of the APIs were in fact being shipped for a legitimate purpose.

The 242 firms described in FDA's testimony were identified by comparing 1999 data from the OASIS database with information in CDER's Establishment Evaluation System (EES) to determine if U.S. dosage form manufacturing firms appear to have received an API from a source not named in their approved application. After electronic comparison and further manual comparisons, this search revealed that 242 foreign firms, which, at this time, do not appear to be approved suppliers for application products, shipped an API to various U.S. firms.

The 242 firms were incorporated into an import alert that issued on October 3, 2000 (IA #6666). These firms will be prevented from importing the specified APIs into the U.S. unless they can provide documentation that the dosage form manufacturer consignee holds an approval for the use of that API in a finished human drug product or documentation establishing that the API is intended for an authorized use (e.g., for a non-application product).

If a firm can show that the API is used in an approved human drug product, then a pre-approval inspection would have been performed, and CDER will search the paper inspection records pre-dating the EES system to confirm the pre-approval or other inspection of the API manufacturer. In other cases, investigations at the domestic firms/consignees are being conducted to determine if APIs from unapproved sources were used to manufacture finished drug products.

While there is no definition of exactly what each investigation will require, our past experience indicates an average of 20 hours is needed for each investigation. We estimate that the average cost is $130.00 per hour per investigator, not including travel costs, administrative and support time.

Mr. DINGELL. How much does an inspection cost of a foreign plant?

Ms. HENNEY. It really depends on the location of the plant, the number of inspectors you have to take along, whether have you to hire translators. There is a varying amount.

Mr. DINGELL. So the answer is you don't know?

Ms. HENNEY. I don't know a precise figure but I will be glad to submit it.

[The following was received for the record:]

The chart below provides information on the costs of foreign human drug process inspections conducted by the Office of Regulatory Affairs (ORA). It uses the fiscal year (FY) 2001 Agency estimated cost of $112,000 per FTE, and travel costs and inspection times approved by ORA as of October 23, 2000.

This information can be used to estimate costs for inspections but does not include an estimate of CDER costs pertaining to the regulatory outcomes of inspections. Each ORA foreign Drug Process inspection requires 2 people at 60 direct hours each. The estimate includes all direct time and travel costs and includes all other indirect costs as well. The total cost for a single inspection is estimated at approximately $23,000 per inspection.

HUMAN DRUG PROCESS INSPECTIONS

(FY 2001 Costs 65846 $112,000 per FTE)

	Hours per Inspection	FTE per Inspection	Salary & Operating Cost ($)	Travel Cost ($)	Total Cost ($)
Lead Consumer Safety Officer (CSO)	60	0.0645	7,224	2,500	9,724
2nd CSO or Laboratory Analyst	60	0.0645	7,224	2,500	9,724
Subtotal Direct inspection Cost	120	0.1290	14,448	5,000	19,448
ORA indirect (support) Cost (.125 FTE)		0.0161	1,806		1,806
Total ORA Cost/Foreign GMP Inspection		0.1451	16,254	5,000	21,254
CDER Inspection Report Review		0.0160	1,792		11,792
TOTAL FOREIGN INSPECTION COST					23,046

Mr. DINGELL. I don't mean to be rude to you, but I've got a lot of questions and a limited amount of time. You have to cooperate.

Isn't it true that FDA has still not developed a specific timeframe for how frequently the agency should be inspecting foreign firms that ship to the U.S. for good manufacturing practices?

Ms. HENNEY. I believe what we would like to have as our goal is to be able to inspect them as we do our domestic plants, which is typically on an every 2-year cycle. Our resources have not allowed that.

Mr. DINGELL. How much resources will it take you to have the resources you need to inspect those every 2 years?

Ms. HENNEY. I will be glad to submit that exact figure for the record.

[The following was received for the record:]

Based on CDER's drug listing data, we estimate that there are now approximately 1,900 foreign firms that may be offering drugs for entry to the U.S. market. If these firms were inspected every two years (at 950 inspections per year), our annual projected costs for inspections, trip planning and evaluation of findings would be approximately $23 million. The table below describes the calculations arriving at this amount, but does not include the cost of any necessary equipment.

This represents only a calculation of direct inspection resources. The actual costs to support a sustained program of offshore inspections worldwide would require inspection organization enhancements and personnel management adjustments. For example, currently we accomplish foreign inspections with inspectors based at field offices in U.S. These inspectors are needed to inspect the domestic industry and travel for foreign inspections part-time. A program of two-year foreign inspections would likely require the restructuring of inspector stationing.

PROJECTED ANNUAL INSPECTIONS COST

Activity	Explanation	Cost
	950 inspections x 0.1451 FTE per inspec. = 138 FTE	
ORA Inspectors	138 FTE x $112,000 FTE cost	$15,456,000
ORA travel planning	10 FTE x $112,000 FTE cost =	1,120,000
Travel	950 inspections x $5,000 per inspection	4,750,000
	gxl950 reports x 0.016 FTE per review = 15.2 FTE	
CDER review	15.2 FTE x $112,000 FTE cost =	1,702,400
TOTAL		$23,028,400

Mr. DINGELL. How many plants abroad have you been able to inspect more than once or meet the 2-year requirement that you are supposed to? You are going to have to submit that for the record, too. But I do want to know the answer.

[The following was received for the record:]

As of October 1, 2000, FDA has conducted 1,507 inspections of the 900 foreign facilities in the CDER database of all firms inspected since October 1, 1994. Four hundred and ten (4 1 0) of the 900 facilities have had multiple inspections in this six-year time period. Two hundred and seventy-five (275) have been inspected twice, 87 have been inspected three times, and 48 have been inspected four or more times in the last six years.

Mr. DINGELL. Now, Commissioner Henney, isn't it also the case that many foreign firms that ship drug products to the United States haven't received a GMP inspection from FDA in as many as 6 to 8 years or longer? Just yes or no.

Ms. HENNEY. It is very dependent upon whether they have an active NDA——

Mr. DINGELL. The answer then is you don't know or the answer to the question is yes or no? Which, please?

Ms. HENNEY. It is not a yes or no answer. It is very dependent on an active NDA or have a drug that is undergoing approval.

Mr. DINGELL. I am talking about good manufacturing practices investigations.

Ms. HENNEY. Good manufacturing investigations are highly dependent on whether they have an application under approval or they have active NDAs.

Mr. DINGELL. Without the 2-year inspection you don't have the vaguest idea of whether or not they are complying with the requirements of good manufacturing practices, do you?

Ms. HENNEY. I think that would be fair to say, that we don't know what goes on in the interval.

Mr. DINGELL. Commissioner, isn't it also the case that because FDA has not visited such facilities that it is possible that GMP conditions may have worsened since the—in such facilities since the last FDA inspection?

Ms. HENNEY. That could always be the case.

Mr. DINGELL. Particularly in countries like China or in some of the new developing countries that are exporting to the United States, isn't that so?

Ms. HENNEY. I don't know that we see a higher rate there but, yes, that could be.

Mr. DINGELL. Now, commissioner, isn't it also true that FDA's attempts to catch up on the backlog of foreign inspections will require additional moneys and resources be made available to enable FDA, first, to catch up and, second, to meet its schedule, isn't that right?

Ms. HENNEY. Absolutely.

Mr. DINGELL. Of course the number of these plants is going to increase, is it not?

Ms. HENNEY. Yes, it will.

Mr. DINGELL. China will have as many as 10 to 15 new facilities that are going to require FDA inspections. I am informed that is in the $15,000 and $30,000 range; is that true or false?

Ms. HENNEY. I think that is a reasonable approximation of what an inspection there costs.

Mr. DINGELL. Now, Commissioner, isn't it generally the case that much of the current backlog in foreign inspections is directly attributable to the lack of sufficient resources?

Ms. HENNEY. Yes.

Mr. DINGELL. The Congress has not been giving you either the money or the personnel you need to do these things, isn't that so?

Ms. HENNEY. Not for the past several years.

Mr. DINGELL. Is it also the case as the agency attempts to inspect foreign firms overseas it risks understaffing its domestic inspections?

Ms. HENNEY. That is of great concern to me.

Mr. DINGELL. Isn't it the case that over the past 2 years FDA always had insufficient resources in the area of foreign inspections?

Ms. HENNEY. We've had insufficient resources in terms of our overall post-marketing surveillance.

Mr. DINGELL. Now, Commissioner, isn't it the case that conducting proper foreign inspections of facilities who send drug products to the United States to determine that they meet current good manufacturing practices is a vital function in ensuring the safety of the Nation's drug supply?

Ms. HENNEY. It is a critical element.

Mr. DINGELL. Now, Commissioner, if FDA is falling behind in their foreign GMP inspections and many plants overseas have not been recently inspected, how much money would it take to get FDA to a point where it is satisfied that it knows the internal GMP conditions of all plants shipping drug products to the United States are in fact complying with our laws and in fact are safe?

Ms. HENNEY. I will be glad to submit that for the record, sir.

[The following was received for the record:]

Ideally, a biennial inspection should be conducted to acquire the information needed to determine compliance with CGMP requirements. Therefore, our best projection of the annual cost to ensure manufacturing quality of imported drugs is $23 million, as described in the answer to question #5.

Mr. DINGELL. I think you are going to have to. Now, Commissioner, in your testimony you say that as many as 242 manufacturers in 36 countries appear to have exported to the United States but have not been inspected. That is a reliable number, is it?

Ms. HENNEY. Yes, to the best of our ability, it is a hard number.

Mr. DINGELL. It is possible, however, that the number is larger, is it not?

Ms. HENNEY. We have——

Mr. DINGELL. Because you really have a big problem there in terms of keeping your data and information on these kinds of activities current, isn't that right?

Ms. HENNEY. Yes, but that data has been processed——

Mr. DINGELL. With all respect, I've got to get through my questions. Commissioner, would you acknowledge that there is a rather serious problem with counterfeiting in both bulk drug ingredients as well as finished products in other parts of the world?

Ms. HENNEY. I think any time you have a product like this that is very profitable, it opens itself up for counterfeiting efforts.

Mr. DINGELL. You are not able to inspect at all ports of entry nor are you able to inspect all mail entries and things of that kind, isn't that right?

Ms. HENNEY. Yes, because of our resources.

Mr. DINGELL. That is true also with regard to your agency, is it not, Mr. Kelly?

Mr. KELLY. Yes, sir.

Mr. DINGELL. Now, Commissioner, if a shipment of finished products were to contain 10 percent counterfeit material and 90 percent legitimate material, isn't it true that a batch test might have some limitations in detecting the counterfeit part of the shipment?

Ms. HENNEY. Yes, it would depend——

Mr. DINGELL. Would you indicate whether you agree with that statement, Mr. Kelly?

Mr. KELLY. As far as batch testing is concerned?

Mr. DINGELL. Yes. You are going to have a hard time if you've got part good and partly counterfeit or part deteriorated, you are going do have trouble telling which is good and if you only batch test or if you only do some subject to sampling, you are going to have trouble knowing what the real facts are with regard to that shipment, isn't that right?

Mr. KELLY. Yes.

Mr. DINGELL. Now, Commissioner, does batch testing give you 100 percent reliability that the product coming into United States does not have counterfeit product mixed into it?

Ms. HENNEY. I think it would depend on the degree to—the percentage the——

Mr. DINGELL. The answer simply is no, unless you inspect it all, isn't that right?

Ms. HENNEY. That would give you greater assurance, yes.

Mr. DINGELL. Commissioner, does batch testing give you 90 percent reliability that a product coming into the U.S. doesn't have counterfeit product mixed into it or 80 percent or 70 percent? Can you give us an idea what the figure is or do you wish to submit that?

Ms. HENNEY. I would prefer to submit it for the record, sir.

[The following was received for the record:]

Quality testing of each batch of bulk drugs would provide some valuable information on potency, purity and other specifications. A counterfeit bulk drug, however, might also meet these specifications and such testing could not be relied upon to detect certain counterfeit products.

A program that includes chemical fingerprint testing and evaluation of labeling, containers, seals, certificates of analysis, shipping records and covert markings will be more useful in detecting and deterring shipments of counterfeit bulk drugs. It is not possible at this time to determine the statistical probability of detecting counterfeit drugs using these samples and analytical techniques.

Mr. DINGELL. I want you to understand, Commissioner, these are friendly questions. I have been a critic of the fact that the Congress has not funded your agency for a long time. So I don't want you to engage in any defensive behavior here. I think we have to do something to see to it you can protect the people. I am not satisfied that the effort now ongoing in the Congress is going to enable us to have assurances on that matter.

Commissioner, isn't it the case that certain products are inherently difficult to repackage or relabel, such as sterile injection solutions, auto injectors, ointments, and prefilled syringes?

Ms. HENNEY. Yes, those are some of the most difficult.

Mr. DINGELL. So—and what—how do you know whether the repackagers abroad are repackaging safely in cleanly and adequate circumstances or they are repackaging pharmaceuticals that in fact meet all the Food and Drug standards, including being current on their efficacy and not having passed their expiration date?

Ms. HENNEY. That is one of our greatest challenges in this whole area.

Mr. DINGELL. How many of these repackagers do you investigate?

Ms. HENNEY. I would be glad to submit——

[The following was received for the record:]

Sixteen foreign facilities classified as drug repackagers have been inspected since October 1, 1994.

Mr. DINGELL. How many of them are there and how often do you get around to visit them? If you'll submit that for the record, too.

[The following was received for the record:]

There are approximately 102 foreign facilities identified as repackagers in the current CDER drug registration and listing database. Drug repackagers have been included in the tier of facilities generally scheduled for routine surveillance once every six years under the system currently applied to target and assign foreign inspections. Some of these facilities will be inspected more frequently if they are covered by a pre-approval inspection of if they are classified as violative.

Mr. DINGELL. Commissioner, it is my understanding that drug packaging, drug labels, holograms, and even shipping records are often easily copied by counterfeiters and that the sophistication of the efforts of counterfeiters make it extremely difficult to determine faked items from the real items, is that true?

Ms. HENNEY. We have a better chance to catch them with those, but they can get one step ahead of us, yes.

Mr. DINGELL. Mr. Kelly, do you agree with that statement?

Mr. KELLY. Yes, sir.

Mr. DINGELL. Commissioner Henney, what percentage of bulk raw materials used to manufacture globally is considered counterfeit? I believe you gave us some figures earlier. Would you like to do that again, please?

Ms. HENNEY. I think that to our best estimate and knowledge it is probably in the 5 to 7 percent range.

Mr. DINGELL. Now you have a problem not only with the fact that it is—that these are counterfeit but also that they might be deteriorated, contaminated, adulterated, filthy, full of foreign or deleterious or other hazardous additions to the mix, is that not so?

Ms. HENNEY. Yes.

Mr. DINGELL. Mr. Chairman, I think I've taken all the time I am entitled to. I thank you for your curtesy.

Mr. BURR. The gentleman's time has expired, but the Chair would notify the gentleman to stick around with us.

Mr. DINGELL. I thank you. Commissioner Henney and Mr. Kelly, I want to thank you. I did not mean to be discourteous. Our time, as you know, is limited. We have a great deal that we have to do to get a proper record here.

Mr. BURR. The Chair would take this opportunity to recognize himself for the purposes of questions.

Again welcome to all our witnesses. Commissioner, let me ask you what standard do we currently use to determine whether a drug that is coming into this country, imported into this country, has met our standards? Do we use section 505 of the Food Drug Cosmetic Act?

Ms. HENNEY. Yes, that is primarily the standard we rely on.

Mr. BURR. So we currently use that standard for all drugs that are imported into this country.

Now, Mr. Kelly, is that the understanding that the Customs agency has?

Mr. KELLY. Yes, sir, that is our understanding.

Mr. BURR. I need you to pull that mike closer for her purposes when we move to you. General Maher, let me ask you, is the Justice Department clear on the standard that we use for approving drugs for import into this country?

Ms. MAHER. We wouldn't be doing the testing.

Mr. BURR. What part would you play in the determination of drugs coming into this country or reimported into this country?

Ms. MAHER. I am not sure I understand the question. We don't play a role in determining——

Mr. BURR. Do you play a role as it relates to patent protection? Is the U.S. code something that comes under your jurisdiction?

Ms. MAHER. It does not come specifically under my jurisdiction.

Mr. BURR. But under the Justice Department?

Ms. MAHER. Yes.

Mr. BURR. Are you familiar with title 35, section 271 of the U.S. Code?

Ms. MAHER. I am not.

Mr. BURR. Let me basically tell you what that says. And just get—I've got the code here in case you want to read it for yourself. But what that code says, "whoever without authority makes use of, offers to sell or sells any patented invention within the United States or imports into the United States any patented invention during the term of the patent therefore infringes on the patent." Is that your understanding of the law?

Ms. MAHER. As I said, I am not familiar with that provision but——

Mr. BURR. Given what that provision says, would it then be a patent infringement for a manufacturer to produce in this country for export, not for the purposes of reimporting into this country, and a third party reimports into this country without the explicit consent of the manufacturer; have they infringed on the manufacturer's patent?

Ms. MAHER. I would assume so if there is not a license agreement.

Mr. BURR. If there is not a license agreement that specifically allows them to reimport into this country. That isn't limited just to drugs, isn't it?

Ms. MAHER. No, I don't believe so.

Mr. BURR. That is a general patent protection we have in this country. It is not only stated in the U.S. Code, it to some degree is codified in the North American Free Trade Agreement and in the world Trade Agreement, World Trade Organization as it relates to the TRIPS agreement, where we negotiate intellectual property. So if in fact the FDA for any reason looked at the Justice Department and said as it relates to a patent infringement we want you to sort of wink, turn your head and not enforce this, would that be a precedent in court for other industries as they took to a court a patent infringement against them that you hadn't enforced this one?

Ms. MAHER. I don't think a lack of prosecution can ever be offered as precedent, that somehow it undermines another prosecution. There is always—there are always decisions that have to be made about which cases to bring. The fact that one case isn't brought doesn't undermine a prosecution if the facts and circumstances warrant it in another case.

Mr. BURR. Mr. Kelly, has Customs ever stopped a product because of a patent infringement?

Mr. KELLY. Yes, we do, and it is usually a result of a what you might call a patent lookout where the patent holder would put us on alert as to the possibility of violation.

Mr. BURR. Were you aware before the last hearing we had that it was a patent infringement for the reimportation of pharmaceuticals?

Mr. KELLY. No, sir, but I wasn't at the last hearing either.

Mr. BURR. Hopefully somebody briefed you relative to the line of questions that took place and that was one of them. I think Customs acknowledged that they were not aware that there was a patent violation that existed, whether it is in bulk, API or whether it is in personal use. In fact, it is a patent infringement because it is not specifically or explicitly said that it could be reimported.

Commissioner, let me ask you if I could, given that you use the 505 standard for the current importation of drugs, and let me reask Chairman Bliley's question, do you anticipate that if there's legislation that moves through this institution this year that the FDA would demand section 505 be met before any reimportation language was supported by the FDA?

Ms. HENNEY. Well, section 505 is really the basic safety standard.

Mr. BURR. I think we can get by with a yes or no, given the limited amount of time.

Ms. HENNEY. That all drug approvals must meet. As I tried to indicate to Chairman Bliley, I believe that same standard would apply.

Mr. BURR. So section 505 should apply to any reimportation, yes or no?

Ms. HENNEY. I think we would have that expectation, yes.

Mr. BURR. As you know, a couple of months ago five drug companies joined in the United Nations initiative to provide AIDS drugs to a number of Africa nations at significantly discounted prices. First question, do you have an opinion regarding the impact legalizing reimportation will have on drug manufacturers who either donate or sell drugs in foreign countries below market prices?

Ms. HENNEY. I don't.

Mr. BURR. Have you stopped to think about it at all?

Ms. HENNEY. That is not something I've given consideration to, no.

Mr. BURR. Do you believe that if we lift the reimportation ban that in fact we may actually discourage manufacturers from participating in these types of programs because we've opened up a new market for a drug that meets the 505 standard, designated for some type indigency program, whether it is in Africa, Asia, and potentially it is more profitable for those countries to reimport those drugs to the United States? Should that be a concern to the FDA?

Ms. HENNEY. We have not been asked to consider that question. So I would only be given——

Mr. BURR. Would you supply for this committee a statement from the FDA, a written statement on that?

Ms. HENNEY. I will be happy to.

[The following was received for the record:]

The legislation, as enacted (section 745 of P.L. 106-387), provides in new section 804 (k) of the Federal Food, Drug, and Cosmetic Act (FD&C) Act that the authority to reimport pharmaceutical products does not apply to drugs donated to charitable organizations or a foreign country. This provision should ensure that donated drugs would be used for their intended purpose rather than being resold in the United States.

Mr. BURR. Thank you very much. Commissioner, let me just point out a few things in your testimony if I could. Do we all acknowledge that the growth in international trade over the past few decades has had a substantial impact on the ability of the FDA to cope with the volume of regulated products coming into this country? That is out of your statement.

Ms. HENNEY. I think there are two issues there. Yes, we are seeing an overwhelming exponential increase in the number of regulated products coming into this country, approximately 14 percent I believe just this past year.

Mr. BURR. You've asked for——

Ms. HENNEY. It did stretch our resources tremendously.

Mr. BURR. You've asked for $23 million to fund any effort that might deal with reimportation. Can you break down for me how those $23 million are spent, how much would be enforcement, how many would be inspection?

Ms. HENNEY. Yes, I will be glad to supply that for the record.

[The following was received for the record:]

The President has not yet requested the $23 million, as required by the statute. However, the enclosed chart reflects FDA's estimated cost to fully implement the Medicine Equity and Drug Safety Act of 2000. As you can see, the $23 million for the first year included funding to begin to build the system called for in the bill. Specifically, $2.52 million will go toward beginning to build the Forensic Chemistry Center's drug database; $9.55 million will be used to purchase laboratory equipment and ramp up our laboratory capability; $5.50 million will be used to begin needed information technology upgrades; $5 million will go towards establishing appropriate accreditation capabilities; and $.56 million will be needed for regulation development.

Seven Year Cost Analysis of the Impact of the Jeffords Amendment

	1st Year		2nd Year		3rd Year		4th Year		5th Year		6th Year		7th Year	
Cost Item	FTE	$ 000	FTE	$ 000	FTE	$ 000	FTE	$ 000	FTE	$ 000	FTE	$ 000	FTE	$ 000
Agency Costs														
Regulation Development														
Proposed Rule	3.0	$ 336												
Final Rule			5.0	$ 588										
Office of Chief Counsel	2.0	$ 224	2.0	$ 235	2.0	$ 246	3.0	$ 385	4.0	$ 537	4.0	$ 561	4.0	$ 584
CDER Costs					26.1	$ 3,732	51.8	$ 7,686	51.8	$ 7,990	51.8	$ 7,686	51.8	$ 7,686
Study														$ 500
ORA Costs														
Entry review					24.3	$ 2,990	48.7	$ 6,253	48.7	$ 6,538	48.7	$ 6,823	48.7	$ 7,108
Product tracking document review					29.2	$ 3,589	58.4	$ 7,504	58.4	$ 7,846	58.4	$ 8,188	58.4	$ 8,530
Documentation review					91.3	$ 11,214	182.6	$ 23,449	182.6	$ 24,518	182.6	$ 25,587	182.6	$ 26,656
Laboratory audits					2.0	$ 246	4.0	$ 514	4.0	$ 538	4.0	$ 561	4.0	$ 585
Surveillance Sampling /Authenticity Testing (10%)					24.5	$ 3,010	49.0	$ 6,293	49.0	$ 6,580	49.0	$ 6,867	49.0	$ 7,154
Post-market Surveillance					10.3	$ 1,265	20.6	$ 2,645	20.6	$ 2,765	20.6	$ 2,886	20.6	$ 3,007
Inspections (Domestic & Foreign)					5.7	$ 703	11.4	$ 1,469	11.4	$ 1,536	11.4	$ 1,603	11.4	$ 1,670
Drug database development	19.1	$ 2,517	19.1	$ 2,622	4.8	$ 586	4.8	$ 612	4.8	$ 640	4.8	$ 668	4.8	$ 696
Investigations (OCI cases)					12.0	$ 1,709	23.9	$ 3,552	23.9	$ 3,693	23.9	$ 3,354	23.9	$ 3,494
Forensic Testing					57.2	$ 8,171	114.4	$ 16,982	114.4	$ 17,652	114.4	$ 16,033	114.4	$ 16,703
Lab Operating Costs														
(Cincinnati, New York, Arkansas)														
Developmental/Equipment		$ 9,550		$ 6,550								$ 4,025		$ 4,146
Maintenance						$ 1,208		$ 1,244		$ 1,281		$ 1,319		$ 1,359
IT Costs														
IT cost OASIS import entries														
Developmental/Equipment		$ 2,500		$ 2,500										
Maintenance						$ 500		$ 515		$ 530		$ 546		$ 563
IT cost for Authenticity import entries														
Developmental/Equipment		$ 2,500		$ 2,500										
Maintenance						$ 500		$ 515		$ 530		$ 546		$ 563
Database Registration		$ 500		$ 500	5.0	$ 614	5.0	$ 642	5.0	$ 671	5.0	$ 701	5.0	$ 730
Accreditation Costs														
Buildings, supplies, admin costs		$ 5,000		$ 6,000		$ 1,000		$ 1,000		$ 1,000		$ 1,000		$ 1,000
Maintenance of MRA w/ NACLA				$ 1,000		$ 1,000		$ 1,000		$ 1,000		$ 1,000		$ 1,000
Total Year Cost	**24.1**	**$ 23,127**	**26.1**	**$ 22,494**	**294.4**	**$ 42,282**	**577.6**	**$ 82,262**	**578.6**	**$ 85,847**	**578.6**	**$ 89,956**	**578.6**	**$ 93,734**

$ FTE Cost Module	FY 2001	FY 2002	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Non-OCI	112	117.5	122.841	128.433	134.288	140.143	145.998
OCI	132	137.5	142.841	148.433	154.288	160.143	165.998

Mr. BURR. Thank you. I appreciate that very much.

Also in your testimony, this is in item 3, excuse me, item 4, put all importers on notice they are required to provide the name of foreign manufacturers. As I stated earlier, the FDA has a long history of sending notices out for their acknowledgment, sign-up, licensing, whatever we want to call it. What's your assessment? Have only the honest people registered? Is that the difficulty?

Ms. HENNEY. Well, I think there are many factors in this. And some of it has to do with time and knowledge and a number of other things. We have put the importers on notice again and we are working with Customs right now to make this a condition of entry. So I think that there will be a much more aggressive step taken for not being compliant with this notice.

Mr. BURR. On page 10 of your testimony you state that the FDA's OCI has a close working relationship with Customs, including a memorandum of understanding providing for all OCI agents to be cross-designated as Customs officers. How many total OCI agents are there at FDA?

Ms. HENNEY. Approximately 150.

Mr. BURR. Can you tell me of the 150 agents which are now cross-designated as Customs officers?

Ms. HENNEY. I will be glad to supply the exact number for the record, but I believe nearly all of them are. There are a few I believe, perhaps in Miami, that aren't but they actively work these cases.

[The following was received for the record:]

As you know, the Office of Criminal Investigations (OCI) was established in March 1992 with the selection of a Director. At that time there were no criminal investigators employed by the FDA. In May 1993 FDA and Customs signed an MOU concerning the cross designation of OCI special agents as Customs officers. As a new criminal investigative agency that would be working a number of joint investigations with the Customs it was apparent that our field agents should quickly develop a close working relationship with Customs agents. Therefore, the main purpose of establishing the MOU for cross designation was to achieve a close working relationship and coordination between OCI and Customs. That close working relationship was established and OCI and Customs have in the past and are presently working together on a number of joint investigations.

Cross designation requires a block of training by Customs field offices and a renewal every six months of the cross designation status. OCI currently has a total of 133 special agents and supervisors. Eleven of those agents/supervisors are assigned to OCI headquarters and 122 agents/supervisors are assigned to field offices. Of the 122 agents/supervisors, 77 are crossdesignated as Customs officers. In some cases the initial training or renewals requested by OCI have not taken place for a variety of reasons. Since we have already established a close working relationship with Customs field offices some field supervisors in Customs do not feel cross designation status is necessary for all OCI agents. They conclude that the status should be accorded for a specific reason or investigation, if necessary, citing the time and expense to cross designate agents. Also the language of the MOU states, "The U.S. Customs Service agrees: to designate certain special agents of the Food and Drug Administration, Office of Criminal Investigations as Customs Officers". After years of working with and establishing an excellent cooperative working relationship with Customs field offices, it is FDA's belief that it is not necessary for all OCI agents to be cross-designated as Customs Officers.

OCI investigates numerous import-related cases in virtually every district in the U.S. and Puerto Rico. To our knowledge, the absence of cross-designation has never been a factor or an impediment to any OCI import related case in any district. OCI's relationship with Customs is such that if it was determined that cross-designation was necessary to assure any import investigation was enhanced, OCI would seek it and we are confident that Customs would be responsive.

Mr. BURR. Let me say that according to the information from the U.S. Customs Service that there are presently 15 FDA cross-designated agents in Baltimore, 14 in Los Angeles and 12 in Chicago. That is a total of 41. None of these are in the high volume API districts that you stated. Why aren't all OCI agents cross-designated and why aren't any OCI agents cross-designated in the high volume API areas?

Ms. HENNEY. Well, Mr. Chairman, your information differs a little bit with mine and so I will be glad to supply a fuller answer for the record. Because it has been my understanding——

Mr. BURR. Is that your understanding, Mr. Kelly? I mean these are Customs documents.

Mr. KELLY. My understanding it is the number is about 50. My understanding also is that we do have a close working relationship, close——

Mr. BURR. Are any of those 50 designated in the high volume API districts?

Mr. KELLY. In the locations that you mentioned.

Mr. BURR. Chicago, Baltimore and Los Angeles, which were none of the cities that were mentioned earlier that were high volume.

Mr. KELLY. My understanding is we have a closer working relationship than we had in 1993 when that memorandum of understanding was signed and that we are working in those higher volume ports, even though there is not an official cross-designation working together.

Mr. BURR. The Chair's time has expired. At this time the Chair would recognize the gentleman from California, Mr. Waxman.

Mr. WAXMAN. Thank you very much, Mr. Chairman.

As you know, Commissioner Henney, the House and the Senate both passed drug reimportation language by wide margins as part of the agriculture appropriations bill. Draft compromise language has been circulated and many of us are concerned that the compromise as drafted contains loopholes that the drug companies will exploit to eviscerate the original intent of the proposal.

I and my colleagues Congressman Sanders, Berry, and Crowley wrote to the agriculture appropriations conferees expressing our concerns about the draft language. I would like to ask you about some of the issues we raised in our letter. The letter indicates that the current language appears to allow drug manufacturers to discriminate against U.S. pharmacists and wholesalers. For example, the companies could require their foreign distributors not to sell to U.S. pharmacists or wholesalers and could enforce these requirements by inserting restrictive provisions in their contracts.

Isn't that correct?

Ms. HENNEY. Mr. Waxman, that issue, if it exists, I think could be a real one, but I think that the implications in terms of trade restriction or trade restraints are really better answered by other agencies. We've got a lot of legal advisers.

Mr. WAXMAN. I wasn't really asking before whether this would stand up under NAFTA or GATT or anything else. I am just asking you if the drug companies had a contract with their foreign purchaser not to turn around and sell it and that contract were upheld, that would be a problem, wouldn't it, for importation of drugs into the United States?

Ms. HENNEY. One would think it would.

Mr. WAXMAN. And it would allow, I believe, drug companies themselves or their intermediaries to discriminate against U.S. pharmacies or wholesalers because they could insert these clauses into the contracts with the foreign distributors, which make it illegal then to sell to U.S. pharmacists or wholesalers. And under the current draft of this language in the agricultural appropriations bill, this type of restrictive contract, as I read it, would be perfectly legal. Of course, if we try to challenge it on a trade basis, that could take years before we see any result. We may not win it.

Is there any reason to believe the drug companies would take actions like trying to get these special provisions in contracts with their purchasers abroad?

Ms. HENNEY. I don't know that I have any evidence of that. But if that would happen, I would think it would certainly be something that should be addressed now if Jeffords is expected to work.

Mr. WAXMAN. In fact I believe these restricted practices are commonplace. I agree with you if we are going to face this problem, we ought to correct it now.

If we don't address this loophole, this legislation won't go very far in addressing the high cost of prescription drugs for seniors in the U.S.; and if the language is left as is, it will allow the drug companies to evade the intent of the law.

Another loophole I am concerned with deals with labeling. Drugs must bear the FDA-approved labels. In cases of brand name drugs, the copyright of these labels belongs to the manufacturer. The manufacturer could frustrate the intent of this legislation by using foreign labels that are different than U.S. labels and then refuse to allow reimporters to use the FDA-approved label. Do you think the drug manufacturers could thwart the intent of the law simply by changing labels, their foreign labels?

Ms. HENNEY. We at the FDA did raise this labeling issue to Senator Jeffords soon after it passed on our appropriations bill. We assumed that it was an oversight, but there is nothing in the bill, as you note, that requires the manufacturer to give the approved label to the importer. Without this requirement, then the importer wouldn't have access to that approved label and it couldn't be imported because it would be essentially misbranded. It is likely an issue dealing with copyrights, trademarks and the like, and again it is another thing that needs to be fixed if Jeffords is expected to work.

Mr. WAXMAN. I would think that it is quite simple for the drug companies to use this tactic. Currently labels for the drugs used overseas do not always use the FDA-approved label. If this problem isn't addressed, as you pointed out, drug companies will have an enormous tool to block reimportation of drugs and undermine the intent of the law. It seems to me that there are simple solutions. Prescription drug manufacturers could be required to provide importers with authorization to use approved labeling and manufacturers could be prohibited from discriminating against U.S. pharmacies and wholesalers.

Would you support such an effort to eliminate these loopholes?

Ms. HENNEY. I think they must be worked out if the law is going to work.

Mr. WAXMAN. Thank you.

Mr. Chairman, I yield back the balance of my time.

Mr. UPTON. Thank you. I appreciated your testimony this morning and particularly, Dr. Henney, I was delighted to see the statement in your testimony, I think it was point four, that indicated that the FDA would require manufacturers to notify FDA when they receive poor quality bulk drugs. This was an issue that we took up in our hearing earlier this spring, and as we have proceeded to other things like Firestone, notification to a Federal agency I think is very, very important. How quickly and under what parameters do you see this happening? What timeframe?

Ms. HENNEY. I think we certainly need to engage in a very thorough discussion and dialog with the industry on this matter. It clearly would require rulemaking and notice and comment. Rulemaking could take us several months.

Mr. UPTON. But you expect to see this happen by the early part of next year?

Ms. HENNEY. I think we will begin engaging in these discussions. I don't believe that we could be to a final rule by the first of the year.

Mr. UPTON. I have a question that I would like to sort of set out. In a letter back in July to me, July 25, the FDA wrote, "OCI is willing to work with Customs on a criminal investigative task force if warranted. However, the establishment of a task force is predicated on identifying a large number of specific criminal violations that are occurring and the need to respond to those violations with the resources of a number of agencies." It goes on to say, "In the case of counterfeit bulk drugs, no large number of specific criminal violations has been identified. Accordingly, FDA has concluded that a joint standing task force with Customs for counterfeit bulk drug investigations is not warranted at this time."

Now, a letter that I think the Department of Justice sent to Chairman Bliley a week or 2 ago indicated that in fact an interagency cooperative such as a task force can be an important component of law enforcement, and facilitates the investigation by using each agency's area of expertise.

Where exactly are we in the field of things trying to get all three agencies to work together and in fact develop an interagency task force? Does your language back in July still stand based on what the Department of Justice sent us and as a former OMBite, where was the clearance process?

Ms. HENNEY. I think with respect to the working groups or task forces that are meeting, whether or not it is a standing task force or not may be the term of art we are all debating about.

We clearly are engaged in fairly frequent discussions with a number of parts of Customs with respect to the counterfeit issue both in terms, as I mentioned before, of our laboratory efforts, our importation efforts, our civil actions as well as criminal actions. We simply don't have at this point a standing criminal task force, but we do have a working group that is engaged in fairly frequent meetings. In fact, I attended one in August.

Mr. UPTON. Ms. Maher?

Ms. MAHER. Well, looking at the letter you referred to, and we said that in the Department's view interagency working groups and task forces are effective and can be useful, is the language you quoted, in law enforcement in identifying and in working on particular cases with Customs and FDA. But I don't think that there is any conflict with what the Commissioner has said that we are not currently participating in such a task force.

Mr. UPTON. Do you know how many foreign firms appear to have shipped misbranded products in 1999? Is there any idea? Do you have some list?

Ms. HENNEY. I don't think that we have a list, no.

Mr. UPTON. The FDA indicated that it was developing intelligence on international distribution channels of counterfeit and unapproved drugs. Exactly how is that being done? Is it through the Office of Criminal Investigations? Are they working closely with Customs?

Ms. HENNEY. Mr. Chairman, with your indulgence I would like the person that you gave such worthy praise to before to answer that question. The head of our field operations, Mr. Dennis Baker. If anybody can live in reflective glory, I was very glad that I hired him when I first came on board.

Mr. UPTON. Welcome back.

Mr. BAKER. Thank you.

Mr. UPTON. I have to quickly swear you in.

[Witness sworn.]

Mr. UPTON. You are under oath as well. Thank you.

Mr. BAKER. Mr. Chairman, we have several ways and venues of developing intelligence. We have international working groups where we do have international partners that our Office of Criminal Investigations works with to identify potential counterfeiting operations and distribution throughout the world.

We also evaluate foreign inspections. As an example, our staff are now securing information on all manufacturing that occurs in establishments overseas, not just information on what is being distributed.

Mr. UPTON. Let me stop you right there. In the hearing that we had earlier this summer, we talked a little bit about the glycerin I indicated in my statement, the glycerin which was contaminated in Haiti, which caused a good number of deaths there.

As I recall from that testimony, in fact we traced that back and we found some of that product, at least the raw material, had been identified as coming in and was in the United States and had not been used and it was caught in the nick of time.

Now, did that come from China? Where did that material come from? It came from China. Was any attempt ever made? Whatever happened to the investigation? Here is a substance that caused deaths for sure. Whatever happened to the investigation of where it came from? Did they identify the source where it came from? Was there some tracking?

Mr. BAKER. They did identify the import source into the United States and they did quite a bit of leg work. I would have to pull the files to refresh my memory on it. That was some time ago. We did find it in distribution channels in the United States.

Mr. UPTON. Was that case ever referred to the Department of Justice?

Mr. BAKER. Insofar as the importer?

Mr. UPTON. Correct.

Mr. BAKER. I would have to go back and look at the files to see what the disposition was.

Mr. UPTON. Here is a clear case for what Dr. Henney was indicating in her testimony of requiring the manufacturer—if this had been a U.S. firm, to in fact pass that along directly so that we could take some type of action and make sure that it didn't happen again and in fact identify the source, whether it be FDA inspectors that would go there or have the authority to look out for that company's particular products as they entered the States. Do you know more based on that note that was handed to you there?

Mr. BAKER. We did meet with the Chinese embassy to disclose information that we learned from the Haitian event. In essence, we passed along our information to the Chinese authorities for use against the manufacturer of the product in China.

Mr. UPTON. Do you know if any follow-up happened?

Mr. BAKER. I would have to check to see what the follow-up was.

Mr. UPTON. I would appreciate that for the record.

Mr. BAKER. I will be happy to supply that.

[The following was received for the record:]

On October 28, 1999, Agency representatives from the Division of Emergency and Investigational Operations, Division of Field Science, and Office of International Programs, met with representatives from the Chinese Embassy to disclose the results of the Agency's investigation into the 1996 incident in Haiti that killed 88 children caused by contaminated glycerin used in a drug product. After the Haitian tragedy, FDA issued an Import Alert for glycerin exported from all countries.

FDA began investigating this incident per the request of the World Health Organization. The Agency's findings revealed that the glycerin used in Haiti was contaminated with approximately 24 to 26% diethylene glycol (DEG). The Agency also concluded that the contaminated glycerin, labeled as "pharmaceutical grade", originated from a firm in China. The Agency was not able, however, to identify the firm in China that caused the contamination.

In an effort to bring closure to this issue, to alert Chinese officials to the Agency's findings, and to allow Chinese officials to continue this investigation, the Agency requested the meeting to disclose the results of its investigation.

Embassy officials indicated that they would report back to the Chinese government and initiate a follow-up. FDA officials also offered to assist the Chinese government in their efforts. To date, the Agency has not received any requests for assistance.

Mr. UPTON. Okay, I think that completes my questions at this point. Mr. Bryant.

Mr. BRYANT. Thank you, Mr. Chairman. Dr. Henney, let me ask you a question about what the administration's position would be on reimportation or importation of drugs which are identified in the Controlled Substances Act as drugs which have the potential for addiction or abuse?

Ms. HENNEY. I'm sorry, I heard the first part of your question but not the last part.

Mr. BRYANT. What is the position of the administration and FDA on the reimportation of drugs that are listed on the controlled substances list, those that are addictive and can be used in an abusive way?

Ms. HENNEY. Are you—let me just ask a point of clarification, Mr. Bryant. Are you speaking of the reimportation bill currently being considered or are you talking about personal reimportation of scheduled products?

Mr. BRYANT. The former.

Ms. HENNEY. The former. I don't think that the position as outlined by the administration distinguishes between scheduled products versus prescription drugs. It is really drugs that are manufactured, are under prescription that could be reimported. So I assume that the authors of the legislation mean all products that can be obtained under a prescription and of course some of those are drugs that can be abused.

Mr. BRYANT. I am concerned and I think a number of questions have been asked between the Customs and FDA of the efforts of the joint investigations, cross designations of FDA's OCI, and folks with Customs. Coming from a limited law enforcement background as a former U.S. attorney, and I think I pointed this out in the last hearing, back in June, of the turf battles that go on among investigators, Federal and State investigators. I want to be careful that both of you, and I am sure that Justice would agree, that everyone work together on this in a cooperative fashion so we can make sure whatever we do in Congress works with whatever laws you enforce now are enforced and there are not problems with jealousies among agencies.

I think you testified that 150, most of whom are cross-designated, I am concerned about the location and we don't want to micromanage, but Director Kelly, Mr. Kelly, what is your view on the placing of these—I know that you have folks out there, but the placing of these OCI agents particularly among the high traffic areas, the high volume areas?

Mr. KELLY. Congressman, I am led to believe by our people that we are working more closely now with the FDA than ever before. In 1993 there was a memorandum of understanding that allowed for this cross-designation and there were some issues in 1993 that I think all reports have been resolved. We don't necessarily need this cross-designation because we are working so closely at many of these ports. There certainly is no resistance on our part to expand the cross-designation. The number is about 50, as Congressman Burr mentioned before. If more cross-designation is needed, we will do two.

All of the feedback that I have received is that we are working closely and cooperatively as far as investigations. We do have a task force of sorts in the San Diego area doing Internet investigations right now.

Mr. BRYANT. Would you explain to me in your testimony, maybe on your website, in our preparation materials the indications are that there are something like 358 ports of entry and 20 customs centers in addition to that which you operate, and the issue I would ask you to explain to me, are some of these limited in terms of commercial trade and if we pass this legislation that we are talking about where it would likely increase the importation of drugs and all of the problems that need enforcement, how will that affect those commercial sites and can we close down some of those given the assets that you have, and will you be forced to try to shut down some of these commercial entries to offset that?

Mr. KELLY. We have 301 ports of entry. The overarching supervision are 20 customs centers. Some ports, yes, are strictly trade. For instance, Otai Mesa in California is 10 miles from San Ysidro, it is passenger car, but Otai Mesa is all vehicle traffic. We would—

we simply don't know the volume that will be generated by this piece of legislation. I could not make an intelligent statement whether or not we would be forced to close. That certainly would be a very drastic measure to close a port of entry. We would resist that tremendously.

Mr. BRYANT. We are sort of on both sides of this. We don't want to impair our legitimate businesses but we don't want these counterfeit drugs coming in either. You guys are where the rubber meets the road.

Let me go back to a question, if I can find it very quickly here, to Dr. Henney. Dr. Henney, in terms of the foreign drug plants, our committee here has obtained evidence of some Chinese firms that readily ignore patent laws and distribute these drug products. Are we aware of the distribution of such drug products outside of China that violate our patent laws?

Ms. HENNEY. Mr. Bryant, I am going to have to submit that response for the record. I don't know that I can give you a full and complete answer to what extent we are knowledgeable about that.

[The following was received for the record:]

FDA is not aware of evidence that Chinese firms are manufacturing and distributing pharmaceuticals in violation of U.S. patent laws.

Mr. BRYANT. Mr. Kelly, do you have any information on that?

Mr. KELLY. No, sir.

Mr. BRYANT. This committee has obtained reports of firms that are counterfeiting drug products still under the U.S. patent laws. These firms do manufacture other products that are exported to the United States and it seems to me that the FDA would find these reports relevant to assessing the integrity of these firms, and I assume that the FDA would like to have these reports that the committee has found.

Ms. HENNEY. We would appreciate that.

Mr. BRYANT. Dr. Henney, let me ask you a question here. The FDA seems to be saying that it doesn't want individual citizens to bring drugs approved for the U.S. market from Mexico for their personal use because the agency can't assure the safety and effectiveness of these drugs, but as long as a wholesaler-importer provides documentation about testing products obtained in Mexico, this somehow is dispositive. So while it is not safe and effective if it is brought into the United States by an individual, it seems to be safe and effective if brought in by a commercial operator whose products will be available to not just one person but thousands of other folks, and we are going to know that the drug is safe and effective by virtue of the paperwork being provided by the very person whose business interests are affected by this. This is at best illogical, and at worst this is downright dangerous.

What is it specifically about the pending importation proposal which has changed the FDA's mind and reversed the agency's clear and heretofore unambiguous position about assuring the safety and effectiveness of these imported drugs?

Did you follow all of that?

Ms. HENNEY. I tried to.

Mr. Bryant, I think there are a number of issues embedded in your question. I think first and foremost, the pending legislation which the administration has made comment on was initiated by the Congress. It clearly does apply to importers, and the importer might be a pharmacist, and we feel that if that is to take place, that our current method of assuring a safety system would have to be nurtured with a new system that we would need to put in place to make sure that the safety issues remain strong.

And that is why we are saying that we cannot accomplish this piece of legislation without full funding to support a new safety system on our part in terms of authenticating what is coming in and making sure that it does meet safety standards. However, this piece of pending legislation does not deal with personal importation and the personal importation policy. So we have not made comment in that regard.

I think it is important to keep in context that the personal importation policy when it was initiated by the agency many years ago was a policy built out of compassion, that there was an overriding concern about people's ability to get product that might be available in another country that was not available here, and it was particularly done at the time of the AIDS crisis when there were no treatments available here and possibly available in some other countries. And we opened it up by policy to allow an individual to bring a personal amount of product into this country, or if they were coming in from a country and had already been prescribed a medication in another country that may not have been available here.

I think that policy has extended over time, and it is now one that people are relying on because of the price issue. We have tried to be understanding of that matter. We do have concerns about it and that is why we try to tell citizens that go into other countries to purchase products perhaps at lower cost, that they do that at some risk in terms of their safety, but we have chosen by enforcement discretion not to enforce the law in terms of their personal desire to purchase that product. But they need to be aware of the safety risk they put themselves at.

Mr. BRYANT. To be clear in my own mind, let me ask that each one of you and probably a close simple yes or no answer might apply. You might have to explain a little bit. Do the three agencies, for lack of a better word, that you represent, each one of you, what is your position on this bill that would—these riders, the Crowley and the Coburn and I guess Jeffords over in the Senate, what is the position? Do you favor the passage of this that I understand would allow the importation of bulk drugs from other countries, large numbers, rather than simply the personal use situation? Do you support this type of legislation? And each of you answer yes or no.

Ms. HENNEY. Mr. Bryant, I believe the administration has made itself very clear in terms of strong opposition to both the Crowley and Coburn amendment on the issue of strong safety concerns that those amendments would represent.

On the matter of Jeffords, I think from the FDA's part, the original Jeffords, and I am given to understand that this has been opened up for a lot of discussion, and I don't know its current state of play, but if we looked at the language as originally embodied in Jeffords, we believed that it was a new system, it could be a workable system, and from our part we could only do it if fully funded.

I think a number of other issues have arisen during the course of discussion, but I don't know the current language of Jeffords as it now stands, so I couldn't comment on that.

Mr. KELLY. Trade has essentially doubled in the last 6 years, and obviously the volume comes right through the Customs Service. We don't have a position on the bill. Obviously we do what we have to do. Clearly we are strapped for resources now. So this legislation certainly has the potential of adding to the volume that Customs has to deal with. All I ask is consideration for the Customs Service as far as resources are concerned.

We have a resource allocation model that we had a consultant do for us, and it is an excellent piece of work. It is workload driven. What we would want to do is take information from the FDA and put it into our resource allocation model and come out with a figure, what do we need to effectively enforce this piece of legislation. So our concern is resource driven, what do we need to do our job as far as this piece of legislation is concerned.

Ms. MAHER. Mr. Bryant, the Department of Justice has not commented on the bill and the Office of Consumer Litigation, which I oversee, is certainly not the only component which would have views on that. If the Department were to provide views, we would have to solicit views from divisions such as the Criminal Division and the Office of International Affairs, and so forth. We can do that, but that has not been done to date.

Mr. BRYANT. Thank you. I yield back the balance of my time.

Mr. UPTON. Mr. Cox.

Mr. COX. Thank you, Mr. Chairman.

Thank you for joining us. I would like to ask about the letter that the FDA sent to the committee addressed to Chairman Bliley and copied to the ranking member, Mr. Dingell. I wonder if you can distribute a copy of that letter to the members and the witnesses. This letter concerns the production of documents to the committee concerning the criminal case that is described in Ms. Maher's testimony involving the prosecution of counterfeit antibiotics from the People's Republic of China.

According to the letter of August 29, the FDA may have violated grand jury secrecy rules by disclosing information which is subject to the grand jury rule 6(e) of the Federal Rules of Criminal Procedure. The letter is unusual in that it is not signed by a lawyer, nor does it reference any petition to the court concerning the use of the material within FDA by anyone other than an attorney for the government. I am assuming, and I will have to ask you this question, that the signatory on the letter, Melinda K. Plaisier, is not an attorney for the government; is that correct?

Ms. HENNEY. That's correct. She is head of our legislative office.

Mr. COX. I take it that you are a medical doctor and not an attorney for the government?

Ms. HENNEY. Yes, I am a physician.

Mr. COX. Rule 6(e) of the Federal Rules of Criminal Procedure requires that this information be handled by attorneys for the government, and it would have to be segregated within FDA, presumably stamped secret, and other precautions would have to be taken so that this information could be kept secret within the confines of the law. It appears that that did not occur. Do you know why?

Ms. HENNEY. Mr. Cox, this matter came to our attention a few months ago, I believe a few days before the committee received this letter, we saw during the course of looking at materials that had been provided to the committee that some 6(e) documents inadvertently may have been transmitted in response to a request before the agency from the committee.

Mr. COX. I need to stop you because I don't understand how that can happen. I don't understand how that information could have been in the possession of anyone not an attorney for the government.

Ms. HENNEY. That is what we are investigating ourselves right now, how it happened.

Mr. COX. How can you conclude that it is inadvertent then?

Ms. HENNEY. Well, it was inadvertent in that it got transmitted to the committee and we are exploring how it happened, not only the transmittal to the committee but how it happened that the 6(e) documents were outside the confines of a secure situation within the agency.

Mr. COX. The people who transmitted this information and who reviewed it for transmittal in the first instance apparently were not attorneys for the government and were not on the grand jury list?

Ms. HENNEY. That's correct.

Mr. COX. So at least facially we have a potential criminal violation. Was there a notification to the Inspector General?

Ms. HENNEY. We have notified the Inspector General, but it is under investigation by our internal investigations group.

Mr. COX. Is that normal for a potential criminal violation?

Ms. HENNEY. Yes.

Mr. COX. That the IG would not handle it?

Ms. HENNEY. Within the agency we have an internal affairs operation. They work closely with the IG of the Department, but they are able to undertake investigations within the agency.

Mr. COX. My understanding of your MOU is that in fact it would be normal for the IG to handle that; is that correct?

Ms. HENNEY. Under the memorandum of understanding as I know it, we notify the IG of any matter like this and they take it under consideration as to whether they want to handle solely the investigation or they work with us in the investigation. We have notified them of that and we have not heard whether they will be entering this particular investigation or not.

Mr. COX. I am attempting to find a copy of it, and I just reviewed it recently and it strikes me that it is abnormal for the IG not to do this.

Ms. HENNEY. As I recall, when this particular memorandum of understanding was entered into with the IG, it was at a time when the agency felt a need to have its own internal affairs unit. We were long delayed in terms of waiting for the IG because of the number of cases that they had under investigation through the whole department, and thus this arrangement was developed through this memorandum of understanding. It is that which we have relied on.

Mr. COX. Does the Office of Internal Affairs comprise non-FDA employees?

Ms. HENNEY. No.

Mr. COX. They are people that work for the FDA. Have any of them worked for the Office of Criminal Investigations?

Ms. HENNEY. They are credentialed as essentially criminal investigators, but they do not report to that office.

Mr. COX. Have any of the people who presently work there formally been in the Office of Criminal Investigations?

Ms. HENNEY. I don't know that.

Mr. COX. The concern is that what we have if we handle it as it is being handled is the people conducting the investigation essentially investigating their colleagues. There isn't the same arm's length arrangement that you would have if you had the IG conducting the investigation. I wonder if the MOU seems on its face, as it does to me having read it, to put this in the lap normally of the IG and the decision was made not to do that.

Ms. HENNEY. The decision was to give this to the Office of Internal Affairs. They would make their normal contacts with the IG and develop the plan for the investigation of the matter.

Mr. COX. This has been going on for months. Where does it stand now?

Ms. HENNEY. I have not received a report on the status.

Mr. COX. The Office of Internal Investigations doesn't have the power itself to convene a grand jury?

Ms. HENNEY. No.

Mr. COX. Or to even get testimony under oath as the IG could. Isn't that right?

Ms. HENNEY. I do not know the extent of their authorities in that regard.

Mr. COX. Can they subpoena documents?

Ms. HENNEY. I don't know, Mr. Cox.

Mr. COX. Are you at all involved in the decision whether to conduct the investigation through the IG or through the Office of Internal Investigation?

Ms. HENNEY. I was involved in the decision that said we needed to investigate this matter thoroughly.

Mr. COX. You did not opine on it going to the IG or Internal Affairs?

Ms. HENNEY. I did not make a designation as to which should, and I think what we have normally done when we have matters within the agency that need exploration is to turn first to our Internal Affairs, and then they consult with their colleagues in the IG as to how it will be conducted.

Mr. COX. Why have you not been briefed on the status of the investigation?

Ms. HENNEY. I am normally briefed on the status of the investigation when the investigators feel that they are at a point where they need to be having me make a decision or need to transmit critical information.

Mr. COX. Is your inference from the passage of a month and some since at least we were provided and presumably the FDA was on notice that it is a complex investigation and that is why it is taking a long time or that there is nothing worth paying attention to?

Ms. HENNEY. I don't know what all might be involved in the investigation at this point.

Mr. COX. I raise this because it is rather clear that in the one criminal matter that we have seen—and this is the only one to my knowledge, the only criminal case that FDA has brought for the importation of bulk pharmaceuticals?

Ms. HENNEY. I believe that is correct. I don't know that for a fact.

Mr. COX. It seems that we have a rather serious internal problem within FDA concerning the handling of the documents. They appear not to have been marked properly. They are being handled by people who are not on the grand jury list. They are not apparently in the office where they belong. Do you know the answer to the question of which office these things came from?

Ms. HENNEY. We do not know at this point the different transmission points within the agency. That is what they are exploring right now.

Mr. COX. Do you believe that in any way the misconduct or mishandling of documents here is related to a lack of funding to the FDA?

Ms. HENNEY. I think we will have to make those judgments once we see the completion of the investigation.

Mr. COX. I will say that it strikes me as extremely improbable that that could be the case. Rather this seems to be a clear case of people not following the rules, and I would hope that it would get some serious attention because I have never seen a letter like the one that came to the committee just—let me ask this: Has the FDA or the Department of Justice made application to the District court that had jurisdiction over this matter where the guilty plea was entered, and so on, that would permit the people who have handled this information within FDA to do so?

Ms. HENNEY. I need the thrust of your question again, please.

Mr. COX. Even though I realize, Ms. Maher, you are with the Civil Division, do you know the answer to that question?

Ms. MAHER. I don't know the answer to that question. I just notice that the letter was copied to the Assistant U.S. Attorney in New Jersey. Frankly, this is the first time I have seen the letter, and I wasn't aware of the issue and I don't have any information on it. But that doesn't mean that the U.S. Attorney's office isn't—hasn't made some kind of application. I just don't know the answer to the question.

Mr. COX. Okay. These are very serious matters. It is a crime, and it seems to me, or at least according to 6(e), handling documents in this way is subject to serious criminal penalties. It doesn't seem to be being handled internally with that gravity, and I would hope that would change. The way that it came to the attention of the committee is highly unusual. I don't think that the committee has ever received a letter like this, not only during my 12 years in Congress, but at all because it is so facially irregular.

To the extent that you haven't been briefed on it, I would assume that this would be a good time and perhaps you can get back to us. Is that acceptable?

Ms. HENNEY. Yes.

[The following was received for the record:]

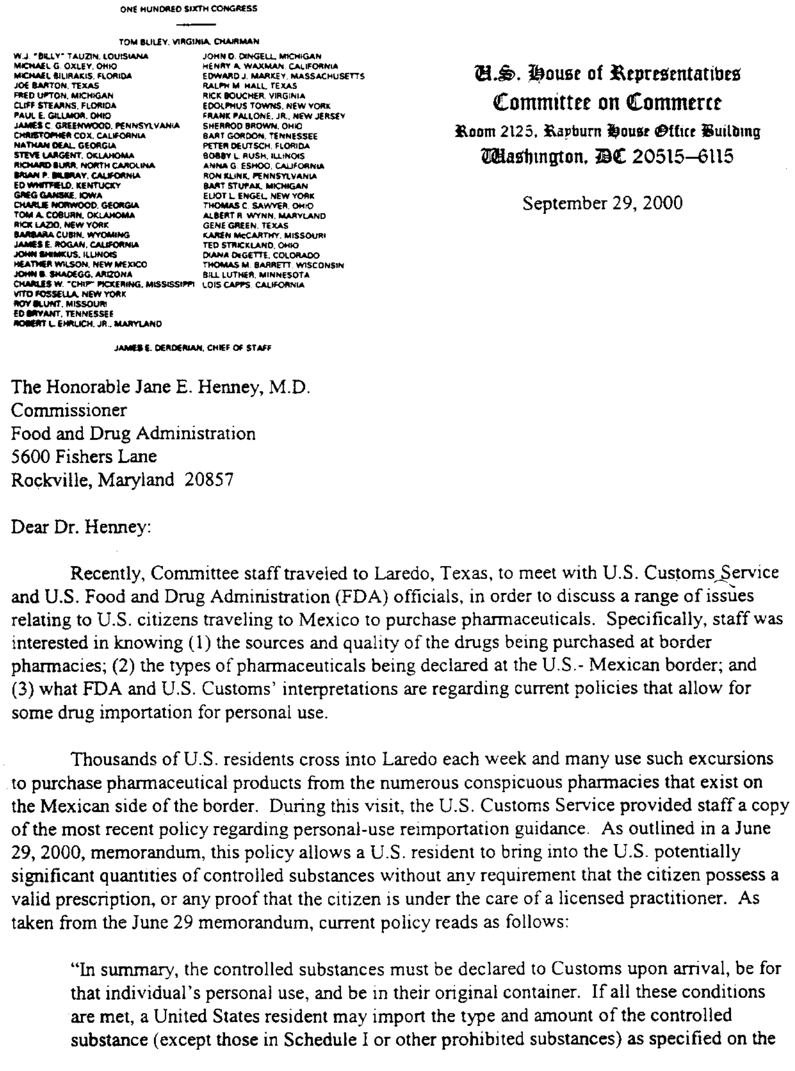
As you know, FDA's Office of Internal Affairs began the preliminary investigation of this matter in September and in accord with our MOU with the Department of

Health and Human Services Office of the Inspector General (OIG) notified them. Subsequently, on October 4, the OIG notified the Agency that they would assume the lead on this investigation. Dr. Henney, Commissioner of Food and Drugs, was briefed on this status subsequent to the hearing. Since the OIG now has the lead, FDA expects no further briefing until the investigation is completed.

Mr. COX. Thank you. Thank you, Mr. Chairman.

Mr. UPTON. Before I yield to Dr. Coburn, I have been asked by the minority to put two letters into the record by unanimous consent that they, I guess, referred to in their questions. So without objection that is now done.

[The following was received for the record:]



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U.S. House of Representatives
Committee on Commerce
Room 2125, Rayburn House Office Building
Washington, DC 20515–6115

September 29, 2000

The Honorable Jane E. Henney, M.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Henney:

Recently, Committee staff traveled to Laredo, Texas, to meet with U.S. Customs Service and U.S. Food and Drug Administration (FDA) officials, in order to discuss a range of issues relating to U.S. citizens traveling to Mexico to purchase pharmaceuticals. Specifically, staff was interested in knowing (1) the sources and quality of the drugs being purchased at border pharmacies; (2) the types of pharmaceuticals being declared at the U.S.- Mexican border; and (3) what FDA and U.S. Customs' interpretations are regarding current policies that allow for some drug importation for personal use.

Thousands of U.S. residents cross into Laredo each week and many use such excursions to purchase pharmaceutical products from the numerous conspicuous pharmacies that exist on the Mexican side of the border. During this visit, the U.S. Customs Service provided staff a copy of the most recent policy regarding personal-use reimportation guidance. As outlined in a June 29, 2000, memorandum, this policy allows a U.S. resident to bring into the U.S. potentially significant quantities of controlled substances without any requirement that the citizen possess a valid prescription, or any proof that the citizen is under the care of a licensed practitioner. As taken from the June 29 memorandum, current policy reads as follows:

> "In summary, the controlled substances must be declared to Customs upon arrival, be for that individual's personal use, and be in their original container. If all these conditions are met, a United States resident may import the type and amount of the controlled substance (except those in Schedule I or other prohibited substances) as specified on the

> prescription.... If the controlled substances are declared, but the United States resident does not possess a valid prescription issued by a practitioner as defined above, the United States resident may bring in only an amount not to exceed 50 dosage units. Remember that the 50 dosage units amount applies to each type of controlled substance being imported. In other words, if the resident is importing 3 different types of controlled substances, the resident may import up to 50 units for each type for a total of 150 dosage units...."

As part of this visit, Committee staff also met with Dr. Marvin Shepherd of the College of Pharmacy at the University of Texas. In 1996, Dr. Shepherd completed a study entitled, *"Examination of the Type of Pharmaceutical Products Being Declared by U.S. Residents Upon Returning to the U.S. From Mexico at the Laredo, Texas, Border Crossing."* That analysis focused on the types of pharmaceuticals being reimported by U.S. citizens from one specific location on the border by examining declaration forms. Given the apparent laxity of the reimportation policy as applied to potentially dangerous drugs, some of the findings in this study raise troubling questions. Several excerpts from the executive summary of Dr. Shepherd's analysis are as follows:

> "A total of 5,624 declarations were analyzed.... The average age of people who completed the declaration forms was 34.5 years. Males were found to be younger than females (33.2 years versus 34.8 years). The median age for males was 33 years, and for females it was 35 years. People over 50 years of age only represented 9.3 percent of the sample and people under the age of 40 represented over half the people declaring drug products. Thus these findings do NOT support the assumption that the majority of people who purchase pharmaceutical products in Mexico and declare the products at the U.S. Customs port of entry are elderly."

The report then goes on to note following:

> "There was an average of 2.48 drug products listed on each claim form. The top 15 drug products listed by number of people declaring a product was as follows: 1. Valium, 2. Rohypnol, 3. Tafil, 4. Tenuate Dospan, 5. Neopercodan, 6. Diminex, 7. Asenlix, 8. Tylex, 9. Darvon, 10. Nubain, 11. Qual, 12. Halcion, 13. Ritalin, 14. Ativan, and 15. Somalgesic. Valium was claimed by 69.8 percent of the people and another benzodiazepine, Rohypnol was declared by 42.6 percent of the people. All the products in the top 15, except Solmalgesic, are classified in the U.S. as "controlled" substances. These results show that the most popular drugs being declared are sedative/hypnotics, antianxiety agents, stimulants and narcotic analgesics."
>
> "Less than two percent of the declared products were for the treatment of cardiovascular problems and only 42 claims out of the 5,624 claims were for an antiulcer agent. Only 96 declaration forms had an antibiotic or antifungal agency listed. Thus, it can be seen that drugs being brought across the border and being declared were not for people who suffer from chronic health conditions such as hypertension, ulcers or cardiovascular problems."

Finally, the report indicates that at least at the time of the study,

> "... on average, 11,000 Valium tablets were being declared a day; this extrapolates to approximately four million Valium tablets per year. For Rohypnol, over four thousand tablets were found to be declared each day and this extrapolates to 1.5 million tablets a year coming into the U.S. These two examples point out that large numbers of pharmaceutical products are being allowed into the U.S. And, when one realizes that many of these products have tremendous abuse potential and some are not even approved by the FDA for use in the U.S., the seriousness of the issue becomes more pronounced."

Because this study was published in 1996, certain of the above findings may be different today than when the study was first released. For example, Rohypnol is now a prohibited substance, and thus would not be allowed into the U.S. Nonetheless, as present policy now allows an individual to bring 50 dosage units of many other controlled substances across the border, it is unclear whether the quantity of the controlled substances being transported into the U.S. has fallen, remains the same, or has even increased.

For example, presently, an individual could legally bring in 300 doses of various controlled substances, as long as these were divided into 6 separate drug-types. And as neither the FDA nor the Customs Service appears to track the frequency by which persons are bringing such drugs into the U.S., one could imagine that several trips a week could be made by certain individuals and thus the number could be higher. Most of the controlled substances listed above are available in the U.S. and are relatively inexpensive, so one must question exactly what this policy is designed to achieve. Do individuals really need 50 Valium tablets between the period of when they first reenter the U.S. and the time they see their doctor? What would the logic be for a traveler needing 150 pills of various controlled substances?

I also remain somewhat confused by how the FDA's personal use policy can operate simultaneously with the U.S. Customs Service directive. Which policy actually governs? Under the Food, Drug, and Cosmetic Act, individuals are not allowed to re-import pharmaceuticals into the U.S., unless certain strict conditions are met. That guidance, as posted on FDA's Website, states that FDA should not consider taking enforcement actions against importation for personal use,

> "when 1) the intended use [of the drug] is unapproved and for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means; 2) there is no known commercialization or promotion to persons residing in the U.S. by those involved in the distribution of the product at issue; 3) the product is considered not to represent an unreasonable risk; and 4) the individual seeking to import the product affirms in writing that it is for the patient's own use (generally not more than a three month supply) and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product or provides evidence that the product is for the continuation of a treatment begun in a foreign country."

Because virtually all of the drugs cited in the above study have "approved" versions of their formulation available in the U.S., it is unclear how an individual can transport such controlled substances into the U.S. under FDA's own policy. Does the guidance, as issued by the U.S. Customs Service, simply nullify FDA's guidance? If so, how does the U.S. Customs Service take into consideration the fact that many of these substances are apparently arriving at the border in misbranded or mislabled containers, which makes such drugs in violation of the FD&C Act? Also, does the U.S. Customs guidance consider the fact that the agency has no evidence or guarantee that many of the above products are made in facilities that meet current good manufacturing practices? What is also unclear is why one directive, issued by the Customs Service, allows a traveler to bring in potentially dangerous substances without a prescription, and yet the other policy, as outlined by FDA, requires that some proof be given that the importer is under the care of a licensed practitioner or provides evidence that the product is for the continuation of a treatment begun in a foreign country. Why the difference? Which agency's policy takes precedence at the U.S. - Mexican border?

I am concerned that, in their present form, these practices may be facilitating the easy entry of substances that cause serious harm when not taken under the supervision of a licensed practitioner. Moreover, I am troubled by the general confusion and differing interpretations staff has found in the implementation of U.S. policy on the importation of pharmaceuticals for personal use. I would therefore ask you to address the following questions:

(1) Please explain the personal use guidance policy that is now being followed at the Mexico-U.S. border. It is unclear whether FDA's policy is the standard or whether the policy as outlined in the June 29 Customs Service memorandum (or a combination of the two) is the policy now in place at the border. Please also explain the origin of this policy (whichever one is used) and how it comports with the various import prohibitions under the Food, Drug and Cosmetic Act. Also, does FDA believe the June 29 Customs Service guidance is consistent with the original intent of FDA's personal use import guidance? Please explain.

(2) Has FDA conducted a study similar to that of Dr. Shepherd's that attempts to determine (1) the average age of persons visiting Mexico to purchase prescription drugs, and (2) types of drugs being declared at the U.S. border for reentry under the above-cited U.S. Customs policy? If so, please provide such findings.

(3) Of the 15 drugs outlined in Dr. Shepherd's study, please provide a brief description of (a) the drug's typical pharmacological use (for what conditions it is generally prescribed); (b) whether a generic version of the drug exists today; (c) the average cost of the drug in the U.S. (please provide the average brand name price and the price for the generic version if one exists); and (d) whether 50 dosage units of the drug would be considered a "three month supply" under FDA's application of its own personal use guidance policy.

(4) Does FDA believe that the present policy, as outlined by the June 29, 2000, memorandum, creates a significant opportunity for controlled substance abuse by U.S. residents? Has FDA conducted any analysis to attempt to measure the abuse potential of this policy? Please discuss any analysis FDA has undertaken in this regard.

(5) Does FDA believe that the findings of Dr. Shepherd's study, which focuses on the Laredo, Texas, border crossing, have application to other border communities in Texas, or in other border states such as California, Arizona, and New Mexico? Does FDA have any basis to make such a judgment?

(6) Are there any age restrictions on those individuals allowed to bring controlled substances into the U.S. without a prescription? Under the June 29 memorandum cited above, there does not appear to be a specific age limitation involving importation. Committee staff was told that many college students travel to Mexico to purchase drugs for "recreational use." Please indicate what the policy is regarding age limits and in which guidance documents this is set forth.

(7) It is my understanding that, under Texas law, controlled substances cannot be brought into the State without a valid prescription. Nevertheless, Customs' guidance policy says that, as a general rule, Customs Officers "will not initiate reports of violations to state authorities." Does FDA have any formal effort to coordinate such policies with Texas officials? If so, please describe them.

(8) What is the quality of the drugs being purchased in Mexico and brought back into the United States? Are they of the same quality drugs manufactured in the United States? Do they pose any risks to the U.S. consumer? If so, please explain any analysis FDA may have undertaken in this regard and what risks, if any, may be posed.

(9) It does not appear that FDA or the Customs Service has any formal mechanism to track the frequency or the volume of drugs being imported by any individual. Please explain how the Customs Service and FDA assess whether present personal use guidance policies are being abused by the frequency in which drugs are being imported by U.S. residents.

Thank you for your cooperation with this request. I ask for your response to these questions by no later than Monday, October 30, 2000. If you need any further information, please have your staff contact Mr. Christopher Knauer of the Commerce Committee Democratic staff at (202) 226-3400.

Sincerely,

JOHN D. DINGELL
RANKING MEMBER

cc: The Honorable Tom Bliley
Chairman, Committee on Commerce

ONE HUNDRED SIXTH CONGRESS

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JAMES E. DERDERIAN, CHIEF OF STAFF

U.S. House of Representatives
Committee on Commerce
Room 2125, Rayburn House Office Building
Washington, DC 20515–6115

July 14, 2000

The Honorable Jane E. Henney, M.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Henney:

Recently, the House of Representatives adopted two amendments, one by Rep. Crowley (D-NY) and one by Rep. Coburn (R-OK), to the Agricultural Appropriations bill which could have a profound effect on how the Food and Drug Administration (FDA) protects consumers from imported prescription drugs of uncertain safety and effectiveness. I am concerned that these amendments could seriously undermine the Prescription Drug Marketing Act (PDMA), and thus adversely affect public health.

During the 1980's, the House Energy and Commerce Committee conducted a lengthy investigation into the foreign drug market that ultimately led to enactment of the PDMA. That investigation discovered a potentially dangerous diversion market that prevented effective control over the true sources of merchandise in a significant number of cases. The integrity of the distribution system was found to be insufficient to prevent the introduction and eventual retail sale of substandard, ineffective, or even counterfeit pharmaceuticals. As the resulting Committee report stated, "pharmaceuticals which have been mislabeled, misbranded, improperly stored or shipped, have exceeded their expiration dates, or are bald counterfeits are injected into the national distribution system for ultimate sale to consumers."

The PDMA was designed to restore the integrity and control over the pharmaceutical market necessary to eliminate both the actual and potential health and safety problems before injury to the consumer could occur. Again, the Committee report was clear on why the PDMA was needed:

> "[R]eimported pharmaceuticals threaten the public health in two ways. First, foreign counterfeits, falsely described as reimported U.S. produced drugs, have entered the distribution system. Second, proper storage and handling of legitimate pharmaceuticals cannot be guaranteed by U.S. law once the drugs have left the boundaries of the United States."

Alarmingly, I find little now that suggests that the problem with misbranded, adulterated, or even counterfeit foreign drugs has been solved. I reiterated these concerns with respect to the Crowley and Coburn amendments (see enclosed remarks). In fact, the evidence suggests the problem is getting worse. I am concerned that in our haste to find a way to bring cheaper drugs to seniors and other needy Americans – a clearly important and laudable goal – we risk making changes to key health and safety laws we may later regret. I am thus requesting that you quickly provide me with the following information:

(1) Please provide a detailed analysis on how (H.R. 4461 and H.R. 3240) would affect FDA's present operations regarding efforts to prevent misbranded or potentially dangerous drugs from entering the U.S. Specifically, please provide:

(a) a description of how the present system now used by FDA works;
(b) what the present system is intended to accomplish; and
(c) what changes would be required (and the potential effects of those changes) if this legislation passes in its present form.

Please include a discussion of how these amendments would affect the activities of other agencies, such as the U.S. Customs Service, with responsibilities for assuring the safety of imported prescription drugs.

(2) Please determine if either of these amendments would have any effect on FDA's ability to enforce good manufacturing practices (GMPs) in any foreign firms that ship drugs to the U.S. If so, please explain any potential effect on consumer health and safety.

(3) Please provide a full description regarding what a "warning letter" is and how it is typically used by the FDA. Please compare this with correspondence that is sent by Customs.

(4) It appears that these amendments would directly affect the ability of FDA to send warning letters to consumers that purchase drugs over the Internet. As you know, some web sites appear to be covertly linked to foreign drug suppliers. When a consumer orders from such a site, it is not always obvious that they are dealing with an offshore supplier, and thus a potentially non-FDA approved facility. Often, warning letters may be the only indication that the Internet-ordered drugs originated from a foreign (and potentially dubious) source. Please indicate how this legislation could affect FDA's ability to protect consumers who purchased drugs in this way.

(5) Please detail any other potential effects this legislation could have on FDA's ability to protect consumers from potentially dangerous drugs that originate abroad.

(6) Finally, please provide technical assistance in the form of specific suggestions for legislative or regulatory changes that would be needed in order to facilitate the safe importation of prescription drugs by individuals, wholesalers, or retailers.

I would appreciate a full response to this letter by Friday, July 28, 2000. Please do not delay.

Sincerely,

JOHN D. DINGELL
RANKING MEMBER

Enclosures

cc: The Honorable Tom Bliley, Chairman
Committee on Commerce

The Honorable Donna E. Shalala, Secretary
Department of Health and Human Services

Mr. COX. Mr. Chairman, I would ask also by unanimous consent that we include the letter that we just had discussion on for clarity purpose.

Mr. UPTON. Without objection, so ordered.

[The following was received for the record:]

DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
August 29, 2000

The HONORABLE THOMAS BLILEY
Chairman, Committee on Commerce
House of Representatives
Washington, D.C. 20515-6115

DEAR MR. CHAIRMAN: This letter is in follow-up to a telephone conversation I had with Mr. Alan Slobodin, Senior Counsel, of your staff on August 25, 2000. I called Mr. Slobodin to advise him that it recently came to our attention that the Food and Drug Administration (the Agency) may have inadvertently disclosed documents related to a closed grand jury investigation in a document production responsive to your letter of August 4, 1998, requesting information about counterfeit bulk drugs.

Specifically, documents provided to the Committee on the following dates, included documents that may be subject to Rule 6(e) of the Federal Rules of Criminal Procedure: October 14, 1998 Boxes 1 and 2; October 29, 1998 Box 3 of 4; December 29, 1999; January 20, 1999.

We respectfully request that if the Committee is finished with these documents, please return them to the Agency. We will be happy to arrange for a courier to pick them up. If the Committee has further need of the documents, we respectfully request that you take precautions to not further disclose, make no copies, and advise us when you are finished so we may arrange to have them returned to the Agency.

We apologize for any inconvenience this may have created. Please let us know when the Agency may retrieve these documents.

Sincerely

MELINDA K. PLAISIER
Associate Commissioner for Legislation

cc: The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce
House of Representatives

Mr. Richard Schechter
Assistant U.S. Attorney
Department of Justice

Mr. UPTON. Dr. Coburn.

Mr. COBURN. Thank you, Mr. Chairman.

Dr. Henney, you have been through a controversial period of time where you approved a drug that Mr. Waxman is happy with and I am unhappy with, and my purpose is not to berate you in that decision, but I have some questions about that process that I think are important for the FDA, and implicit in past drug approvals and future drug approvals, and I just wanted to ask you some questions about that if I might. If you don't know the answer, that is fine. I would like you to get back to me with the answer.

Also, I sent you a letter on September 6 asking some specific questions that I have not heard any answer from, and this was prior to the release of that approval.

The basis of my question is this: With the approval of RU-486, it by itself will not accomplish the purpose under which it was approved by the FDA. It is a recognized medical fact that it has to be used in combination with some other drug with which to do that. The other drug that is used in that is a drug that is produced by G.D. Searle Company, which they have disallowed and disavowed that they want that drug used for that.

My question to you is: Coming with implicit approval of RU-486, will the FDA hold harmless every practitioner in the off-label use for Cytotech for every purpose outside of the approved use and every other drug that might be utilized in combination with other approved drugs, and have you set a precedent which will diminish the power of the FDA?

Ms. HENNEY. With respect to the treatment plan that you reference, Mr. Coburn, Dr. Coburn, I think that the treatment plan in order to accomplish the early termination of pregnancy really does require the two products; and in that regard we have been engaged in discussions with Searle about changing the label to reflect that treatment plan on the label.

In terms of——

Mr. COBURN. Could I interrupt you there? Have you ever in the history of the FDA gone to a manufacturer when they have expressed a desire that they don't want a label change and recommended to them that a label and nonapplication by them be changed because the FDA wants a change? Has that ever happened before in the history of the Food and Drug Administration?

Ms. HENNEY. I don't know the full history of the Food and Drug Administration, so I don't know the answer to your question. I do know that it is quite common in my own field where a drug in and of itself is not the whole treatment, but requires the use of many other drugs to really complete an effective treatment plan, that that has been done in those kinds of situations. And that has been done in those kinds of situations.

Mr. COBURN. But the FDA has, in fact, asked other manufacturers to change their labeling request to make a treatment plan, and that would be your testimony, that the FDA has done that in the past?

Ms. HENNEY. I don't know that there has been a formal request of that to be reflected on the label. There is certainly an acknowledgment, as we have approved different products, that they are a part of a treatment plan, not effective in and of themselves to the degree the treatment plan provides.

Mr. COBURN. In regards to Cytotec, Searle sent a letter out to all practitioners throughout the United States, all providers, stating, No. 1, they don't want this drug used for this, that it's dangerous for this; and in statements made to the press they stated, in fact, that this letter was written jointly with the help of the Food and Drug Administration. Is that a true statement?

Ms. HENNEY. I think there are two issues there. There were essentially two letters in question. One—and we certainly were very much engaged with their writing of the language in the letter that tells practitioners and women really that if they are taking Cytotech and wish to remain pregnant, that there are side effects potentially of birth defects.

However, for the termination of pregnancy, that is a different issue and a different letter under question. And we have asked for revision of that, because it is different than what the company implies and states on its label in other parts of the world.

Mr. COBURN. In fact, under the label requirements, even the IND and the NDA that was done with Cytotec in this country we have no label request and no indication for the procedure under which this drug indirectly has been approved by the FDA in conjunction with RU-486; is that correct?

Ms. HENNEY. What are you talking about here?

Mr. COBURN. I'm talking under the jurisdiction—you don't have jurisdiction outside of this country in terms of labeling. You have jurisdiction in this country.

I'm talking about the letter that they sent—I'd like to introduce this into the record—August 23, which they claim was written in part with the help of the Food and Drug Administration.

So my question is, it really doesn't have anything to do with RU-486 and Cytotec. The fact is, I see a prostitution of the process of the Food and Drug Administration that undermines your ability in the future to ever counter a claim for any drug company that wants a liability claim on off-label using, because in fact the Food and Drug Administration, with its approval of RU-486, has implicitly approved a drug for which the drug manufacturer doesn't want it approved, has stated they don't want it approved, and you helped write a letter that helped them say that.

So my question is, is this all about posturing for liability so that Searle is not sued, and all the liability for using this drug now stated, that should never be used for pregnant women or for abortion, is that to shift all the liability to the practitioner?

In other words, I don't understand why we would not have approved this drug as a true drug regimen and done it in a way that does not dilute the future potential of activity for the FDA to control drugs. And it seems to me that we've diluted your capability precedent for future actions on other off-label drugs because you've implied, I believe, that it's okay to use this drug for this procedure.

Is that a fair statement or an unfair statement?

Ms. HENNEY. We have said that the treatment plan—we have approved the drug as a part of a treatment plan. I think with respect to the matter of helping in terms of drafting of that particular letter, I think we might question that. Our real assistance came in an earlier letter.

Mr. COBURN. So let me make sure I understand this.

The FDA did not assist Searle in this letter to practitioners stating that they do not want Cytotec used for both the induction of labor or as a use of a second drug combination as an abortive fashion.

Ms. HENNEY. It was really for the use of this, if a woman desired to remain pregnant. It was not for its use as an abortive agent.

Mr. COBURN. But I'm talking about this letter. There is no assistance by the FDA with G.D. Searle Company in developing this letter that went to every practitioner in the United States disavowing the utilization of Cytotec, the second component in a medical abortion, that they did not want, should not be used, it is dangerous to be used in that manner. That is the manufacturer of this product saying that, and the FDA had no part in the formulating or drafting of this letter.

Ms. HENNEY. We had a part in the formulating and drafting of the letter that essentially warned health practitioners and patients if Cytotec was used and a woman desired to remain pregnant that she would be at risk of severe birth defects. That is the part of the letter that we assisted in.

Mr. COBURN. Fine. Thank you.

I'd like to submit with unanimous consent this letter from Searle, as well as statements from the press relating to FDA's concerted help in writing this letter. I'm not sure we have a full explanation of why the FDA would have been involved in this.

The other thing that concerns me—and I would make this note in the record for the future, and I think it's very important—FDA has to be the final approver on medical uses and labeling for drugs, and I believe that that process has been bastardized with this letter and with the use of Cytotec in conjunction with this.

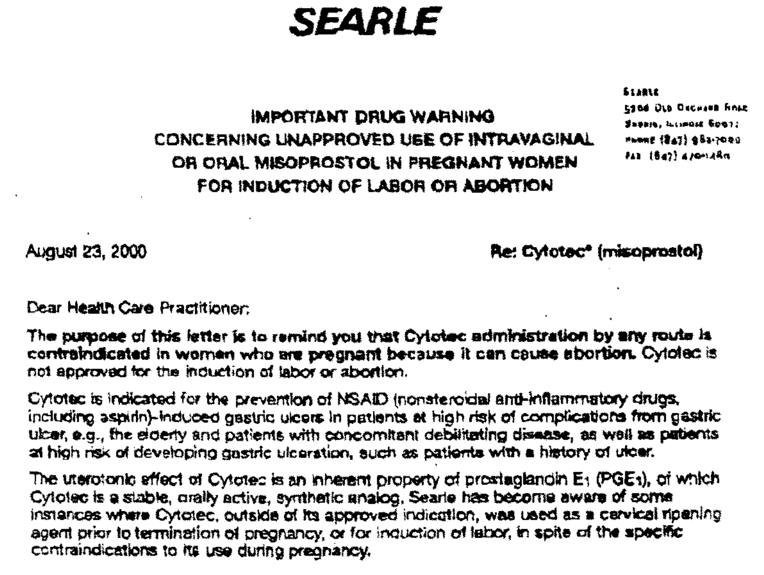
We need to make sure that we preserve FDA's power, and I believe a precedent has been set with this because we now have the Food and Drug Administration asking a manufacturer to allow a drug to be used off-label by their implicit approval of another two drug combinations when, in fact, the manufacturer doesn't want any part of it and doesn't want the liability associated with it.

The second point I would make is because this has happened, any practitioner who uses Cytotec to perform a medical abortion, if there is any complication, Searle is off the hook, and the maker of RU-486 is off the hook, but the practitioner isn't. So what we have done is shifted responsibility from those that should be to those that are carrying out what is recommended by the Food and Drug Administration as a proved policy of terminating lives in this country and doing so in a manner that shifts the liability away from those that should have it.

With that, I thank the chairman for allowing me to participate.

Mr. UPTON. The documents, without objection, are included as part of the record.

[The following was received for the record:]



SEARLE

Searle
5200 Old Orchard Road
Skokie, Illinois [illegible]
Phone (847) 982-7000
Fax (847) [illegible]

**IMPORTANT DRUG WARNING
CONCERNING UNAPPROVED USE OF INTRAVAGINAL
OR ORAL MISOPROSTOL IN PREGNANT WOMEN
FOR INDUCTION OF LABOR OR ABORTION**

August 23, 2000

Re: Cytotec® (misoprostol)

Dear Health Care Practitioner:

The purpose of this letter is to remind you that Cytotec administration by any route is contraindicated in women who are pregnant because it can cause abortion. Cytotec is not approved for the induction of labor or abortion.

Cytotec is indicated for the prevention of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer.

The uterotonic effect of Cytotec is an inherent property of prostaglandin E_1 (PGE_1), of which Cytotec is a stable, orally active, synthetic analog. Searle has become aware of some instances where Cytotec, outside of its approved indication, was used as a cervical ripening agent prior to termination of pregnancy, or for induction of labor, in spite of the specific contraindications to its use during pregnancy.

Serious adverse events reported following off-label use of Cytotec in pregnant women include maternal or fetal death; uterine hyperstimulation, rupture or perforation requiring uterine surgical repair, hysterectomy or salpingo-oophorectomy; amniotic fluid embolism; severe vaginal bleeding, retained placenta, shock, fetal bradycardia and pelvic pain.

Searle has not conducted research concerning the use of Cytotec for cervical ripening prior to termination of pregnancy or for induction of labor, nor does Searle intend to study or support these uses. Therefore, Searle is unable to provide complete risk information for Cytotec when it is used for such purposes. In addition to the known and unknown acute risks to the mother and fetus, the effect of Cytotec on the later growth, development and functional maturation of the child when Cytotec is used for induction of labor or cervical ripening has not been established.

Searle promotes the use of Cytotec only for its approved indication. Please read the enclosed updated complete Prescribing Information for Cytotec.

Further information may be obtained by calling 1-800-323-4204.

Michael Cullen, MD
Medical Director, U.S.
Searle

CY20141A

BIOETHICS & SCIENCE

#5 MISOPROSTOL: SEARLE WARNS AGAINST USE IN PREGNANT WOMEN

G.D. Searle Co. has warned doctors in an Aug. 23 letter not to prescribe its gastric ulcer treatment Cytotec, also known as misoprostol, to pregnant women for the "unapproved use of ... induction of labor or abortion," Health News Daily reports. The announcement comes with the approaching FDA approval for the abortion pill RU-486, or mifepristone. RU-486 calls for a regimen of 600 mg mifepristone, followed by 400 mcg of misoprostol, but Searle "distances itself" from the connection between the two drugs. While Searle admits the inherent "uterotonic effect" of Cytotec, the company maintains that "administration [of the drug] by any route is contraindicated in women who are pregnant because it can cause abortion." According to the company's letter, drafted jointly with the FDA, Searle has "become aware of some instances where Cytotec ... was used as a cervical ripening agent prior to the termination of pregnancy, or for the induction of labor," adding that it will not conduct trials to test Cytotec as an abortifacient. The letter also lists the drug's possible side effects if used in pregnant women -- including maternal or fetal death, uterine hyperstimulation, rupture or perforation requiring uterine surgical repair, hysterectomy or salpingo-oophorectomy, amniotic fluid embolism, severe vaginal bleeding, retained placenta, shock, fetal bradycardia and pelvic pain. Although the FDA may ask Searle to alter Cytotec labeling to lift the contraindication for use in pregnant women as part of the RU-486 review, the company's letter indicates that it may oppose such a change (Health News Daily, 8/28).

Mr. UPTON. Mr. Burr.

Mr. BURR. Thank you, Mr. Chairman.

Commissioner, share with me, if you will, why it has taken 3 years since FDAMA was passed for us to write the final regs as it relates to foreign establishments whose products are imported or offered for import in the United States.

Ms. HENNEY. Mr. Burr, I think that there were probably two factors in its taking 3 years to get this particular regulation out.

The first was that we worked on those matters within the FDA Modernization Act that actually has statutory deadlines or requirements first, and they were given first priority. I would note that we have met nearly 100 percent all of those requirements and requests that are embodied in that law.

Second, we were given no additional appropriations as we were expected to undertake all that is involved in rulemaking. So there were no additional appropriations provided when the FDA Modernization Act passed, so we worked on our—the priority issues first under constrained resources, and it has taken some time for us to get this out.

Mr. BURR. Could this committee expect that any change in our importation or reimportation guidelines in this country would take a similar amount of time, 3 years or longer, to fully implement the regs and the guidelines for that?

Ms. HENNEY. I would hope not. Because we do place a strong priority on this effort. But I have mentioned earlier, throughout the course of this hearing, that we have to prioritize by risk and we have to prioritize by resources.

Mr. BURR. I think you clarified a lot today, and my understanding, and I think the record will show, that the FDA is supportive of a standard that is consistent with section 505, that these drugs must meet.

Mr. Waxman raised a question about labeling, and I would in fact point you toward section 505. And I will just be general in my statement, but section 505 requires that any manufacturer file an NDA. And in that NDA they list those facilities that that specific drug would be made in. And the labeling is determined off of that NDA and in compliance with section 505. For anybody to suggest that there might be an additional labeling issue would be for them to not have an intention to use section 505 as a guideline. Would you agree?

Ms. HENNEY. I don't know that they would have an intention, but yes, they would have to be given some sort of permission or access.

Mr. BURR. Section 505 is very specific as it relates to labeling and the requirement for an NDA and the requirement to list the facilities where one would manufacture a drug, correct?

Ms. HENNEY. You are absolutely correct.

Mr. BURR. You would expect that to also be a guideline that you would follow as it related to reimportation or importation changes that might be considered by this Congress?

Ms. HENNEY. Yes, there would have to be congruency between those two things.

Mr. BURR. Let me go to Mr. Kelly because he is Customs.

Your folks are on the border. I mean, even General Maher said in her testimony there are also drugs that are manufactured in whole or in part in unauthorized factories or facilities and then shipped with the complicity of the authorized manufacturers under its name and trademark—in other words, manufacturers in cahoots with manufacturing outside of the stream of an NDA-named facility.

How do you catch that?

Mr. KELLY. With great difficulty.

Mr. BURR. It is not an expiration date now. It is the correct paperwork; it is the manufacturer's logo; it is everything imprinted—the color of the pill is right. How do you catch it?

Mr. KELLY. As I said, with great difficulty. We need direction, we need to work closely with the FDA to get—we are looking for some national standards now from them to address a lot of these issues.

Mr. BURR. It is tough, isn't it? You can say that. We understand the job that we have got, you are doing. And we understand that as pharmaceuticals become more global, which they are in fact, the challenges that we place on Customs are that much greater.

Now, the natural question that I have to ask is, what is your job going to be like if we allow this new importation and reimportation to exist? How much have we strained your ability for your Customs agents to determine the difference between real and fake, adulterated and nonadulterated?

Mr. KELLY. Well, it clearly will be strained, to what extent we simply don't know. We don't know what the volume is. We don't know what the complexity of these shipments will be.

Mr. BURR. Let me ask General Maher.

Currently, if a U.S. manufacturer manufactures a product and it goes into the consumer stream, they are liable, even if the FDA has approved the safety of, the efficacy of the good manufacturing process, everything is followed; if in fact they have a contaminated product, they are liable. I mean, they will be sued and somebody will win.

Let me ask you, based upon the reimportation language that is out there, if a U.S. manufacturer manufactures in this country for export, it gets out of their chain of control—which everybody's testimony said happens today—it is stored improperly, it is not temperature controlled, it is not humidity controlled, the active ingredient doesn't work because of the storage.

It is reimported back into the country to a wholesaler or pharmacist, it is administered to a patient and their heart medication does not work and they die. Who is liable? Is the original manufacturer liable?

Ms. MAHER. I don't know that I could give you a legal opinion on that, based on the statute.

Mr. BURR. Is that not an important question we get an answer to before we head into this world of saying we will take all drugs from around the world whether they are manufactured in the facility, whether they are stored in the warehouse, whether the manufacturer has been able to maintain that chain of control; as long as we think that it's not contaminated or that it has been made in a facility under section 505, approved, we will take it back in. Are we taking a great risk and aren't we holding private sector companies in this country liable for tremendous exposure?

Ms. MAHER. As I understand it, that is one of the reasons the Jeffords bill, in the version that I reviewed, requires, or will require, the Secretary to issue regulations that would establish a pedigree.

Mr. BURR. We do require the Secretary to authorize the process. We authorize the Food and Drug Administration today to approve the safety and the efficacy of every pharmaceutical in our marketplace. But that authorization, that approval, that good stamp of approval from the FDA does not lift liability from the manufacturers, does it?

Ms. MAHER. I am not suggesting that it would lift the liability. I am suggesting that it would help to identify who is in the chain of custody of the product.

Mr. BURR. And what Mr. Kelly and what you and what the Commissioner have told us today is, we have a serious problem today with counterfeit, adulterated drugs.

Now we are going to open it up to a whole new world, the population is going to get that much bigger, and I only ask you to look at that one piece and tell me whether I am wrong that for a manufacturer of pharmaceutical products in the United States of America who manufactures with the intention of export, and somewhere in the chain of where that drug goes, it is stored improperly, it becomes contaminated for whatever reason, we have not done anything in the language currently debated that would lift the liability from that original manufacturer, have we?

Ms. MAHER. I haven't seen anything expressly in the bill that would do that.

Mr. BURR. I have not either. I would hope that is one of the areas we begin to look at and ask ourselves, in fact, is this fair?

Commissioner, would you agree from my earlier set of questions, that any reimportation or importation of a patented drug without the consent of the manufacturer is in fact against U.S. law?

Ms. HENNEY. Today, yes.

Mr. BURR. And is there anything in the proposed legislation that changes U.S. Code for patent protection of any manufacturer whether they are drug manufacturers or whether they are software manufacturers?

Ms. HENNEY. Not that I am aware of.

Mr. BURR. So even under the current reimportation language, it would have to be the interpretation of whatever department of the Federal Government—hopefully, it is Justice, some area of Justice—that they would look at it and say, it is still against the law to reimport against the consent of a manufacturer under patent protection.

So in fact we have done nothing unless we address in legislation the ability to get around patent law in this country.

Would that be a direct statement to General Maher or to the Commissioner?

Ms. HENNEY. I would think that would be one issue that would clearly have to be worked through.

Mr. BURR. Would you also agree that—would you also agree, it puts us in great jeopardy as it relates to our negotiations for harmonization with the EU on a drug standard, if in fact we get away from the gold standard we have always had, which is section 505?

Ms. HENNEY. I don't know that the legislation under consideration would truly get us away from that standard.

Mr. BURR. As long as we stick to 505, we are okay, we are on sound ground. But any movement away from section 505 is the standard that we use for a sign-off that something is safe and effective to come back into this country would, in fact, put us in great jeopardy with our trade negotiators on harmonization of drug approvals between the EU and the United States of America where we, for 3 or 4 years now, cannot find agreement.

Ms. HENNEY. Mr. Burr, I am going to ask your indulgence in providing a fuller answer to your question for the record. We clearly have been involved in nearly a 10-year discussion in terms of our international harmonization efforts with not only the EU, but Japan and others, about harmonizing what we see in terms of our review documents. And the standard that we expect at the end for us, a standard of approval, may still be different than other countries; but we have never abandoned that standard in all of those discussions.

But I really would appreciate the privilege of providing a full answer for the record.

[The following was received for the record:]

We do not believe the Medicine Equity and Drug Safety Act of 2000 (section 745 of P.L. 106387) would compromise the approval standard in Section 505 of the FD&C Act. Drugs allowed into the U.S. under this legislation are expected to already have been approved by FDA. Therefore, we do not expect any impact on MRA negotiations.

Mr. BURR. I would appreciate that, because I hope that given the interaction that members of this committee have had with the FDA relative to this issue, that our understanding is still the same and that we would hold fast to the gold standard in any harmonization negotiations that we might go through, either with the EU or with other countries.

Mr. Chairman, I am happy to yield back the balance of my time. I want once again to thank our witnesses. I hope they understand that not only are we here to look at the counterfeit problem and to be as helpful as we possibly can be as a committee and as a Congress; we are also here to make sure that any steps that we might make don't contribute to the problem that we have.

And I think clearly there are questions that exist, some of which we have gotten answers to today; and I thank our witnesses for that. But clearly there are many more areas than the authors of this legislation on reimportation have thought of that are affected by what we do; and I hope for once we will slow down, we will work with an agency that up till this point in its history has never broken from the gold standard that it set.

Certainly there is a list of former commissioners of the FDA who have raised questions about what we might be getting ready to do, and I would like to quote one in concluding. It is a letter dated July 17, 2000, to the Senate Majority Leader, Trent Lott, Tom Daschle from former FDA Commissioner Goyan, and I quote, "Even with my background and training, based upon physical inspection alone, I can't tell the difference between an authentic drug that has been properly stored and handled, an authentic drug that has not been properly stored and handled, and a counterfeit medicine that looks exactly like the real medicine that it copies.

"How are the Customs Service agents at entry points along our borders with Mexico or at one of our Great Lakes ports going to tell the difference?"

I think that best sums up the challenge that you have got, Mr. Kelly, but it best sums up the reason that we should slow down and do it right and work in a partnership and not a political vacuum.

I yield back.

Mr. UPTON. I appreciate the gentleman yielding back the balance of his time. I just note for the record, I wasn't intending to go to a third round.

Mr. BURR. I had confidence you weren't.

Mr. UPTON. Mr. Strickland.

Mr. STRICKLAND. Thank you, Mr. Chairman.

Dr. Henney, I find myself generally sympathetic with whatever we can do to lower the price of drugs for American consumers who, I think, are getting gouged with these high prices. Having said that, I think it is terribly important that we make sure that whatever we do protects the American consumer and the American public.

In that regard, I understand this letter from Representative Dingell has been placed into the record; and having read this letter, I am concerned that it appears that there is a major problem, at least along the Mexican border, where substances that probably should not be available to certain individuals are being permitted into the country in significant quantities. By that I mean, I think that ought to be a major concern for us.

What I would like to ask you is, can we expect an answer to the issues raised in this letter made available to this committee within, say, 2 weeks? Is that a reasonable thing to request of you?

Ms. HENNEY. We will make every effort, Mr. Strickland, to respond within 2 weeks. I would say that the investigators or the faculty members that Mr. Dingell cites within the letter, that have done at least a preliminary study on this issue, we actually had invited to come in to talk to the whole leadership group of the Agency about their findings so that we might explore not only what they found, but if there are any other projects, that we might work on them—work with them on.

So I think that we are very sympathetic to this issue, particularly as it relates to the personal importation policy, and we want to find out everything that they have found out in terms of their study and evaluation of the Mexican border.

Mr. STRICKLAND. For example, they indicate that on a particular day, 11,000 Valium tablets were brought into the country. Having worked in health care settings, I know how devastating access to that kind of drug can be if it isn't appropriately monitored by a physician.

And I also understand that every study has particular methodologies and perhaps certain assumptions that need to be looked at and evaluated to make sure that it is a credible study. But I think these are very, very serious findings that are outlined in this letter, and it seems that it would be really helpful if we could have a response from you, and this committee could know what your findings and what your conclusions are regarding these particular allegations.

Ms. HENNEY. Well, I think that they are very interesting findings, not only of the controlled substances that may be being brought in under personal importation that have unique issues, but also that it is not just seniors that are going into Canada—and not just Canada from their study, but Mexico from this study—but it is really much younger people who are seeking these medications as well. So that is why we really want to look in depth as at what is being found.

Mr. STRICKLAND. Just one more question. Is it reasonable for us to expect you will sit down, or your office will sit down, with Customs and try to work together to try to make sure that these issues are resolved?

Ms. HENNEY. We intend to sit down not only with Customs, but with DEA. We do have a policy that harmonizes; sometimes, in operation, it is not interpreted as consistently as it might be. So we want to undergird our understanding about how personal importation, as it relates to scheduled products, really is to work. And certainly we want to share with them the findings of the study.

Mr. STRICKLAND. Thank you.

Thank you, Mr. Chairman. No further questions.

Mr. UPTON. Mr. Bryant.

Mr. BRYANT. Thank you, Mr. Chairman for this second round.

Ms. Maher, let me ask you, you know, so often we hear stories—probably countless stories—about how people in developed countries and underdeveloped countries, taking medication, experience problems with drugs that don't work or drugs that do them harm. And realistically we just don't have that over here in the United States very often.

I am wondering, as we look at changing the policy rather dramatically that would allow potential reimportation of potentially dangerous counterfeit drugs—whatever, the whole gamut of bad things that can happen in this country—it is not unrealistic that we could see some people that are injured, some people that die as a result of this. And I know that is not the intent of Congress. We want to have drugs that are, I guess, more affordable, whatever. I assume that is the logic behind this. I know I certainly do, but again not at the risk of having people die.

Is the Department of Justice—in terms of the current resources you have available, is the Department of Justice that would handle the actual prosecution of these cases that are made by Customs and made by the FDA-OCI folks, are you, with the resources you have now, ready to handle this potential from a legal standpoint?

Ms. MAHER. Well, we are certainly ready, willing and able to prosecute cases involving counterfeit pharmaceuticals. And if, as a result of a new reimportation law, there were to be an increase in those right now, we don't anticipate an inability to prosecute cases. So we are prepared to bring cases that are referred to us involving counterfeit drugs.

I think it is the counterfeit drugs that you are referring to that cause harm to those who consume them. Whether they are in the

United States or in some developing country, they are drugs that are other than what they purport to be.

Mr. BRYANT. I think it almost goes without saying if this law is changed, there will be an increase in the importation of drugs now; and how many of those are counterfeit and defective or whatever are yet to be determined. And there was fear of that at one point; that is why the law was passed as it is. And certainly I think we all understand that the real deterrent to this type of conduct ultimately is the fear of prosecution of getting caught and then being prosecuted to the full force of the law.

Ms. MAHER. These are very resource-intensive prosecutions to bring, and that is why some of the suggestions that were contained in our written testimony are things that we believe would make these prosecutions easier and less time-consuming and resource intensive.

Mr. BRYANT. Dr. Henney, I also practiced law, and I was a civil defense lawyer and defended medical health care providers' malpractice cases, and realistic enough to know—Dr. Coburn kind of woke me up on this. I had expressed some concerns about the approval of RU-486, but I would like to follow up on some of the questions he had—not as a doctor. I am not a physician like you or he are; I am a lawyer. And know just enough about medicine to be fairly dangerous to myself.

But help me out on the FDA approach here. Is—as I understand, this is kind of a two-phase—the first phase is one drug followed up by second-phase drug that Dr. Coburn was alluding to quite a bit.

Now, is this first drug—and I know it has a specific name, is it—where is it going to be manufactured, inside the country of the United States or is it going to be outside?

Ms. HENNEY. Mr. Bryant, there are two drugs involved in this. The first is misoprostol. That is the drug that we announced the approval of last Thursday; and then following that, on the third day misoprostol is taken. That combination in a treatment plan essentially is the combination that results in early termination of pregnancy. We have at the FDA made the determination that we will keep the manufacturing site of this particular product confidential for two reasons.

Mr. BRYANT. Let me stop there. I think I understand some of the politics involved and some of the economic issues involved. Are the two drugs you refer to, is that first and second phase? Because I am looking—where does Dr. Coburn's Searle product come in?

Ms. HENNEY. Day three, that is the second drug.

Mr. BRYANT. So we know who manufactures or who handles the second product, potentially. But the first one, you are saying you cannot tell this committee whether that product—I am not asking, where specifically is it made, other than is it in this country or out of the country; because I am concerned that—I believe if drugs are manufactured in this country generally what the FDA does have, I guess, is some authority over that and some inspection occasionally of the processes to ensure that there is quality control. I don't have that same confidence that the FDA has that for any kind of drug that is manufactured out of this country.

So is it fair to say—let me ask it this way: Is it fair to say that the FDA will have some process or some inspection or some ability to judge the quality of this product and its manufacturing process?

Ms. HENNEY. Mr. Bryant, let me assure you that this product had to go through every step of approval that any drug does approved by the FDA. And that includes the preapproval inspection of all of the processes of manufacture and making that drug. And this drug met that at its manufacturing sites.

Mr. BRYANT. You are not prepared to tell this committee if the manufacturing is outside the country or inside the country?

Ms. HENNEY. No, I am not.

Mr. BRYANT. The second phase that Dr. Coburn questioned, again from a liability standpoint, does the FDA by asking—let's again use Searle as an example. There may be other conditions that would be involved that could have their particular drug used off-label, I think is the terminology. Does the FDA, by approving this entire process, believe it is affording protection from liability to companies like Searle who are involved in that second process either willingly or unwillingly?

Ms. HENNEY. Mr. Bryant, as you alluded to, I am a doctor and not a lawyer. So I don't know the full answer to that question. But we will try to provide a response to you for the record.

Mr. BRYANT. In simple terms, is this the first time to your knowledge that the FDA has ever asked a company such as Searle to, in effect, relabel a product, say, You can use it really for other issues beyond what we say?

Ms. HENNEY. As you know, the FDA has been around for 100 years, and we have been approving products for probably some 50 years. And I just simply don't know the answer to that question.

Mr. BRYANT. So from your knowledge, you just don't know?

Ms. HENNEY. I don't know.

Mr. BRYANT. When you are questioning your attorneys, what would be the liability effect of that? Would you anticipate that Searle, for example, again would have to go back and begin a retesting process for themselves, verify that this is a safe, effective use of their product?

I assume they have done that for the reason the product is used for now, but with you asking them to label it to another use, wouldn't you think they would be wise to at least go back and test it themselves? Or are you providing—is FDA providing them liability from that?

Ms. HENNEY. Mr. Bryant, certainly not liability, but the basis of the test, the clinical trials and specifics under question involve this product both at clinical trials that were part of this submission from the U.S. and France. So we would rely on that information.

Mr. BRYANT. Would you also—and I assume you will have access to this record; if some of my questions maybe are discombobulated, you can determine where I am going about the liability issues.

Would you also give us the opinion of your attorneys, I guess, at FDA in terms of the liability for doctors?

I guess the point he concluded with, even—I am not sure I disagree with Dr. Coburn—is that what appears to be an effort—there appears to be an effort by FDA to protect the manufacturer of phase one drugs, as well as what I call the phase two drugs. That is my wording. And in the end, things do go wrong.

You know, the history that I have read about overseas is—you know, has been pretty good; all that counts. But things do happen and things will happen; and in those instances, you know, people look around for deep pockets. And I am wondering if all that is going to be left out there that could provide some compensation for an injured plaintiff would be the doctors. Dr. Coburn seems to think that. I am not sure that is right, to burden their backs, and—when they are trying to do the right thing, and have you, FDA, out there working with the drug companies to maybe to give them immunity.

I don't know how it will all play out, but could you maybe check and give us a response, your attorney's best guess on that?

Ms. HENNEY. We will try to the best of our ability to give you a response to that.

[The following was received for the record:]

Under the approved treatment regimen, misoprostol is administered on day three to help stimulate uterine contractions. This use of misoprostol is contained in the approved labeling of mifepristone. It is based on the clinical trials for the regimen of the two drugs, which FDA found to be safe and effective for the termination of early pregnancy. FDA does not address liability issues, either for manufacturers or for physicians, in its approval decisions.

Mr. BRYANT. Thank you.

Mr. UPTON. Thank you. I might announce the intent—a vote has been called. I have got a couple of questions that I know I am not going to get through, so I am going to submit those in writing. I am going to ask one or two questions before the next bell rings. And then we will release you all, this panel, we will go vote and probably start the second panel at about 1:15 when we get back.

Dr. Henney, I was very concerned about how FDA handles criminal investigative information; and my question, which I understand your staff, was briefed about last week regards how the FDA in fact handles these investigative leads.

I am going to ask unanimous consent that this internal e-mail from the FDA's Office of Criminal Investigations be entered into the record. This is an e-mail that was dated January 7, 1997, concerning bulk counterfeit issues, and according to the e-mail, FDA received information from its counterpart in Australia, called the Therapeutic Goods Administration, TGA. The information was that the TGA had obtained evidence of a delivery of bulk drug material manufactured in India, supplied to a pharmaceutical manufacturer in Australia, which had been partially substituted with sugar milled to the same size as the bulk drug; and the substitution involved three of ten containers in the delivery.

TGA further determined that the inferior grade active pharmaceutical ingredients were being placed in the bottom of the containers or in every third or fourth drum. Apparently, the firms involved have access to sophisticated packaging activity that may even co-opt employees in the process.

According to the e-mail, the FDA agent was going to contact the TGA, obtain all the pertinent information. The only other information besides the e-mail was a handwritten note on the e-mail indicating the name of the Indian firm and that the FDA had a record of two import entries, one in 1994, but none in 1995 through 1997.

However, the committee's investigation shows that this Indian firm had been inspected twice by the FDA up to that time and that the U.S. in fact was its primary export market. And, in addition, the committee has not received any other documents or information, whether the FDA ever pursued this matter. And I don't believe that the matter had been—even amounted to a preliminary inquiry by the Office of Criminal Investigations, based on the FDA's June 2 letter to Chairman Bliley.

Do you have any information for the committee on whether or not the investigative lead was ever pursued further with the Australians? If so, what happened; and if not, why not? And does the Office of Criminal Investigations close the matter because they relied totally on FDA's information on the import data system?

Ms. HENNEY. Mr. Chairman, I would want to give a full response to your question for the record. I do know that we have a very strong and good working relationship through our counterparts in Australia. And I do know that we did some tracking on this particular issue, but I would like to outline that in full detail, if I could, for the record.

Mr. UPTON. Okay. We will allow you to do that.

[The following was received for the record:]

The OCI e-mail dated January 7, 1997, concerned information provided to OCI by FDA's Forensic Chemistry Center (FCC). FCC was passing information to OCI that they received from the Medicines Control Agency (MCA) of Britain. MCA was made aware of the information in December 1996 during a Pharmaceutical Inspection Convention where the Therapeutic Goods Administration of Australia made a presentation. Other FDA personnel attended this convention. The information concerned a delivery of sulfamethoxazole raw material manufactured in India and supplied to Australia, which had been partially substituted with sugar milled to the same size as sulfamethoxazole.

At the time, a query was made by OCI to determine if the company had imported product to the U.S. That inquiry determined that there was no record of entries by the company for the years 1995, 1996 or 1997. OCI did not open an investigation because there was no criminal violation to pursue. The information regarding the incident was maintained and regulatory offices in FDA were aware of the situation.

Mr. UPTON. We appreciate your testimony, all three of you, as you are now, as they say, "saved by the bell."

We will come back at about 1:15.

[Brief recess.]

Mr. UPTON. Our next panel really includes only Nikki Mehringer, who is the Area Quality Control Leader at Eli Lilly.

Thanks so much for being patient and waiting. I hope you had something to eat, or else a late breakfast. As you know, the rules in the subcommittee—we always have the tradition of taking testimony under oath. Do you have any problem with that?

Ms. MEHRINGER. No problem.

Mr. UPTON. Do you wish to be represented by counsel?

Ms. MEHRINGER. No.

[Witness sworn.]

Mr. UPTON. You are now under oath. Your testimony is made part of the record in its entirety, and if you can limit your remarks to about 5 minutes, that would be terrific.

And the time is now yours. Thank you.

TESTIMONY OF NIKKI MEHRINGER, AREA QUALITY CONTROL LEADER, ELI LILLY

Ms. MEHRINGER. Thank you, Mr. Chairman, members of the committee. Thank you very much for this opportunity to talk with the committee about matters of importance concerning safety and quality.

I am a registered pharmacist, I am a quality control professional, and I am a consumer, I am a voter, I am a wife, and I am a mother; and the testimony I will give today will reflect my experiences in each of these roles.

We have talked a lot this morning about counterfeit, and about people who might want to use changes in the laws and regulations of this country to their advantage. I want to talk about other possibilities that may happen when people who want to follow laws, as they may be changed under the provisions, and still lead to increased risk for American patients.

Let me explain for a few moments the duties of a quality control professional at a pharmaceutical manufacturer. The current good manufacturing practices for finished pharmaceuticals, we have heard about them this morning. They are part of the code of Federal regulations; they are the book by which I do my job, by which I live, by which I am inspected by the FDA.

I want to read just a few fascinating points from this to you. The second paragraph of the GNP states, "The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act, and such drug, as well as the person who is responsible for the failure to comply, should be subject to regulatory action."

This is very important. This is one of the first things we teach people when they come to work in our industry. What this says is, if you don't follow any of these rules, the drug product you have manufactured is adulterated, under law. If it is under your control, you shall reject it. If it is on the market, you shall recall it. It doesn't matter what the test results were; we do not test quality, we build it in through this system.

One more paragraph, "Responsibilities of the Quality Control Unit: There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging, term labeling and drug products and the authority to review production records to assure that no errors have occurred; or if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packaged or held under contract by another company."

That is my job. That is the job of everybody who works for me. It is the job of a person and people at every pharmaceutical manufacturing company. Accountability here is pretty clear: The regulatory action can be taken and, again, these are rules.

This law is a minimum. Every quality control unit at a pharmaceutical manufacturer determines their own internal standards, writes their own policy and procedures, determines what specifications they want to use, which may be higher and tighter than those required by the law. It is a business decision we make, because we believe it gives us an advantage. We believe it is best for the consumer.

Today, nothing enters a U.S. wholesaler or the U.S. Distribution system without the approval of the quality control unit of a manufacturer. This is appropriate. These are the experts with the attributes of that particular drug.

Under the provisions of the bill under consideration for importation and reimportation, the decision on whether or not a drug product can enter or reenter the U.S. distribution system would be taken away from the manufacturer and decentralized to hundreds of wholesalers and pharmacists. The basis for their decision on whether that product could enter or reenter would be a paper trail and some degree of testing that would provide reasonable assurance of the quality of the drug product.

This violates the very basis of quality control principles, that quality is designed in, built in, controlled in and not tested in. And the role of these laws and regulations in this system is very unclear to me.

Let's imagine a few scenarios of how this might work, Mr. Chairman. Let's say you receive a call today from a person in your district who says, I have a complaint on a drug product. A person just called my office, and they do sometimes then say, My daughter took a drug product. She's in the hospital; she had an adverse reaction. It could be from a tablet, a capsule, an injectable product, maybe an aerosol, an inhaler—maybe she had asthma and expected to get some good result in the middle of an attack, and she didn't.

She calls you. She is upset. You know where to go; you can call the FDA. But you can call that pharmaceutical manufacturer, talk to that quality control group. And if it were me, if you called me, I would say, give me 2 hours.

I have all the traceability of that lot. I know where it went, I know where it has been stored, I know everything about that until it got to the U.S. wholesaler. Then I handed it to a wholesaler who is registered, who is covered by the Prescription Drug Marketing Act, who is inspected by their State board of pharmacy; and he has complete records.

By that afternoon, I will tell you the history of that drug, and I will tell you if there is anything wrong with it. You have got clear accountability.

Let's imagine that happens again in 2 years if this is passed. You call me. I say, let me check. And then I call you back and say, You know that lot of drug I shipped out of the country 18 months ago, and I shipped it to a wholesaler out of the country? I never intended it to be reimported back into the U.S. In fact, the labeling I put on it was for the country I shipped it to. I can tell you, the labeling was not suitable for the U.S. market, not approved.

I don't know when it came back. I don't know how it came back. I don't know where it came back. I don't know where it is stored. And I am not sure who to call to find out.

You see the difference. The single point of accountability is very, very clear. And it is what the law charges me with. If we change this, I do not understand how I can have accountability for activities that I have no control over.

The duties with which I am charged trouble me profoundly, that the activities of looking at data regarding storage, devising testing protocols, setting limits, reviewing test results and deciding disposition of batches will be done by hundreds of entities who have no technical knowledge of this drug product.

Every change that is made has intended and unintended consequences. Certainly we know the intended consequences of this provision, but the unintended consequences could be very serious.

We all know it would be sad if people receive very dramatic bodily harm from some counterfeit drug or receive some very dramatic adverse drug event. But I will tell you what is just as sad. What is just as sad is if somebody goes and pays their money and receives a drug that doesn't work and they don't know it is not working and they pay their money and they take it and they never get better. And the doctor doesn't know if it is a treatment failure or a diagnosis failure or a drug failure.

Today, when you go to the pharmacy and you have a prescription filled, you don't worry that it is safe and effective, do you? I don't. I have great faith in the FDA and the whole enforcement system within the U.S. But how sad it would be if we would lose that.

The United States has a good system of control around the manufacture and distribution of pharmaceutical products. It is tedious. It is detailed. It is not always convenient. It is monotonous. People who are in charge of control functions can drive the people around them crazy. But we do it every day in this same controlled manner so that when we need to call on it, when we need to trace a product, if we need to recall a product, we know everywhere that was sent.

We can get our hands on it quickly. It is there. I will tell you that just like good health itself, you don't appreciate this control system until it is gone.

That concludes my testimony, and I have also submitted written testimony for the record.

[The prepared statement of Nikki V. Mehringer follows:]

PREPARED STATEMENT OF NIKKI V. MEHRINGER, AREA QUALITY CONTROL LEADER, EUROPE AND NORTH AMERICA, ELI LILLY AND COMPANY

Thank you for the opportunity to speak with you today regarding Quality Control and Safety matters of interest to the Committee.

Quality control is essential from the initial point of manufacturing through the entire distribution chain to the hands of the patient. Even the healthcare professional cannot look at a white tablet and determine if it will still be effective—we are all dependant on the controls throughout the system that assure the Safety, Identity, Strength, Quality, and Purity of the medicine. A failure in this system may cause failure in treatment, medical harm, and result in significantly increased expense.

I am a Registered Pharmacist and have practiced pharmacy in 4 states (Indiana, Ohio, Iowa, and Illinois). I have 15 years experience in the pharmaceutical manufacturing industry as a Quality Control professional. I am also a consumer, a wife, and a mother. My comments reflect my experiences in all of these roles.

Food and Drug regulation in the United States is based on a three-fold approach:

1. The Law—The history of Food and Drug law in the United States has been based on reactions to public health crises rather than visionary approaches to potential risks. The principal law is the Food Drug and Cosmetic Act, which was passed in 1938 in reaction to a disaster in which a poisonous ingredient was mistakenly used in the preparation of an antibiotic causing the deaths of dozens of children.

Changes in the act have been made over the years, often in response to major public health issues. Examples of these changes include the establishment of Good Manufacturing Practices and the Prescription Drug Marketing Act. As a result, we have a well-constructed system of laws and regulations, which provides the U.S. public with safe and effective medicines. This system is recognized around the world for the extremely high standards it maintains in the areas of drug manufacturing and distribution.

2. Enforcement—the Food and Drug Administration is charged with the enforcement of the Food Drug and Cosmetic Act. The FDA accomplishes this with a system consisting of the following:

a) Drug Registration and Approval—This system of review determines what products may be sold in the U.S., including approval of the product itself, the labeling of the product (including approved uses and safety warnings), the location and methods for the manufacture and testing of the product, storage requirements, and allowed expiration dating.

b) Facility inspections for Good Manufacturing Practices—All FDA-regulated locations, whether within the U.S. or in other countries, are subject to both routine and for-cause FDA inspections. Such inspections may relate to the practices of the manufacturer, including the state of facilities, procedures, organization and education of staff, quality systems, and process controls in place at the facility.

3. Good Science—The Pharmaceutical Industry and the FDA collaborate to improve current Good Manufacturing Practices through scientific approaches such as advancements in validation practices, stability studies of molecules, and new methods of manufacturing and testing.

This three-fold system maintains the assurance of quality that the American consumer demands. The underlying concepts that support this system are complex and dynamic. At the risk of over-simplification, the goal of the entire system is to achieve “Control.” It is no accident that the term we use for the organizational entities entrusted with the duty to run these systems within a factory is “Quality Control.” The systems in place demand control from drug development through manufacturing and distribution to assure that the product is safe and effective for its intended use. Final product testing is only the confirmation that the process worked.

Chart A illustrates a typical supply chain that supplies product to the U.S. Consumer. At each step, there are applicable registration requirements, regulations, and enforcement agencies. At each step, accountability is clear. Requirements for security, identity control, accountability, traceability, and storage are clear. If a consumer registers a complaint, the entire history of that single capsule or vial can be traced and investigated through the system that is in place. The supply chain is controlled.

Why is this control of the supply chain critical? It has been suggested that a drug product could leave this controlled supply chain for a period of time and then be allowed to re-enter it if testing were performed upon re-entry. The inherent limitations of final product testing do not support this assertion. These limitations include the following:

a) Drug products are assigned expiration dates because the drug product itself changes over time. The changes in drug products are dependent on storage conditions, particularly heat, humidity, and sunlight. Testing gives a single-point piece of data regarding the chemical status of that product on that day. To predict the “goodness” or the efficacy of a drug product on its assigned expiry date, one must know the storage conditions, packaging components, and inherent nature of the molecule. The methods and calculations to predict this are so sensitive and complex that the FDA has just published a Stability Guidance Document that is over 100 pages long. Thus, a single point of testing today cannot predict the performance of that product over time unless it is put in the context of the inherent nature of that molecule and the storage conditions that the product has experienced.

b) Final product testing is not recognized by the law or by the industry as sufficient to guarantee safety or quality. In fact, manufacturers reject many lots that meet all testing requirements because they did not meet the requirements of Good Manufacturing Practices for in-process controls, validation, adherence to the approved NDA, or other reasons. A drug product may meet all testing requirements and still be determined to be adulterated or misbranded under U.S. law. Most of the warning letters received by FDA-regulated manufacturers do not involve product that fails to meet testing requirements; instead these warnings are based on suspect practices at the manufacturer. The FDA teaches their investigators to catch potential problems before they get to the point that a product would actually fail to meet testing requirements—the FDA wants that buffer in their control system to prevent potential public health issues. In fact, many lots that meet all testing requirements are later recalled from the U.S. marketplace each year because they are discovered to have not met these GMP requirements or because they failed to meet labeling requirements.

c) Reliability of testing results varies greatly depending on the laboratory that performs the testing, the equipment used, the analytical testing method used, and the education and experience of the people who run the test. To transfer a testing method from one laboratory to another within the same company using similar equipment consumes hundreds of man-hours to assure that the different laboratories will generate similar results on a given sample.

Dismantling the control of the supply chain leads to other concerns around safety and quality. A few of these are listed below:

a) When a customer complaint is received today by the FDA or the pharmaceutical manufacturer, all the records necessary to investigate the lot of product are available immediately. The manufacturer can trace the history of that product from the dispensing of the raw materials, the manufacture of the active ingredient, the manufacture and packaging, storage, and distribution of that single tablet, capsule, or vial. If a recall is deemed to be necessary, the manufacturer can contact all wholesalers to whom that lot of product was shipped within a few hours. If a decentralized system of importation or re-importation were instituted, the manufacturer would not have this capability to trace product. In fact, the manufacturer may be recalling a lot of product in Europe with no idea that any of the product has been shipped into the United States. Additionally, the incident that caused the lot of product to be unacceptable to the consumer may have occurred somewhere out of the control of the manufacturer or the U.S. government, making investigation slow and cumbersome and enforcement impossible.

b) Each country has unique requirements for products sold in that country. Each market has different expectations for products sold in that market. A manufacturer may be approved by FDA and therefore will target certain lots of product for the U.S. market and will manufacture those lots in accordance with FDA and U.S. requirements. However, other lots of product produced at that same facility will be targeted for other countries and will be manufactured in accordance with their requirements. If the pharmaceutical company no longer controls the movement of these materials between countries, then there is risk that the importer will not be equipped or able to discern critical differences in products that may lead to confusion among patients or health care professionals and safety issues. Examples of these concerns include:

1) Labeling requirements—Approval of labeling is a part of the drug approval process in each country. Therefore, labeling is different for each country. Differences may include critical content issues including indications for use and wording of safety warnings and also include convenience issues such as the bar codes used for inventory control in each country. Only the manufacturer can determine if a given label is appropriate for a given market based on the knowledge of the complex registration and customer requirement for each market.

2) Packaging—Once again, packaging is approved as part of each country's drug approval process. Packaging components may look the same, but may be made of different materials. Requirements vary and may have safety implications—for example, the U.S. has strict standards for Child-Resistant containers that may not be approved in other markets. Once again, the manufacturer is charged with assuring that all requirements are met for the intended market. A product may meet all testing requirements but the container may not meet the U.S. government requirements.

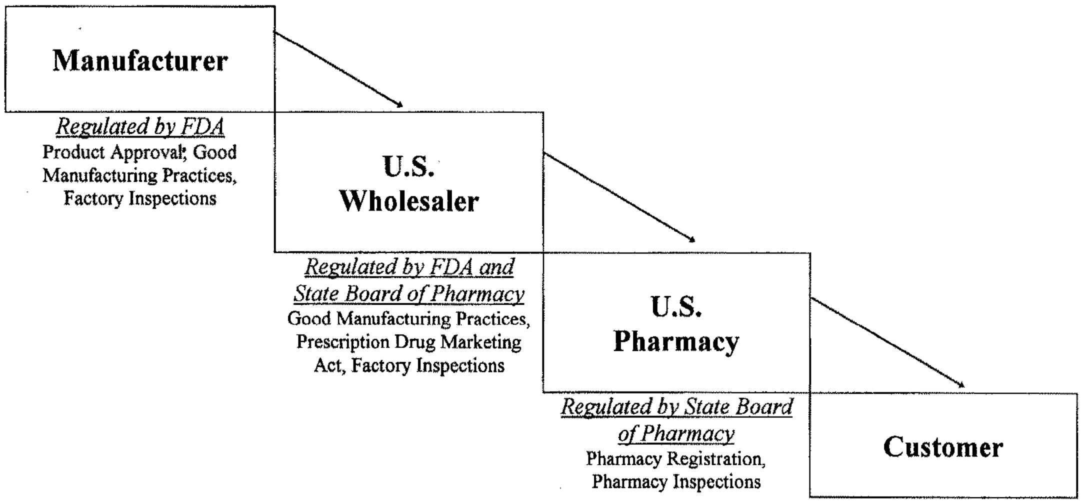
3) Single dose identity or trade dress—Tablets and capsules intended for market in the United States are uniquely identified by color, shape, size, or imprinting upon the tablet or capsule. These unique identifiers are registered at U.S. poison control centers to assure quick identification in case of an emergency. Tablets and capsules intended for market elsewhere may not have these same identifiers. The resulting confusion for health care professionals who depend on this system could be disastrous if an importer was not aware of this difference.

All of the issues raised above demonstrate increased risk to the public health assuming that all involved are making a true effort to transform this system of a centralized, controlled supply chain to a decentralized system where hundreds of different entities may be importing the same drug product into the United States from multiple sources. None of the statements above address the potential risks from those who are looking for an open door to bring product into the country that they know do not meet the requirements of the NDA or Good Manufacturing Practices. Drug counterfeiting is a real issue. The U.S. has been able to minimize the availability of counterfeit drugs through the strict controls in place today. Areas around the world with less strict enforcement capabilities find containers of material that contain placebo, substandard or sub-potent or super-potent drug, or sometimes drugs that are a completely different entity than the label states. The people who participate in this counterfeit business are a sophisticated group who knows how to weigh the potential risk of being caught against the potential benefit. It is in all of our best interests to make sure they know that the enforcement systems in the U.S. will not be weakened and they enter here at great risk.

If any of the potential changes to the supply chain for the U.S. pharmaceutical market lead to product that is dramatically harmful to patients, we will discover it quickly, and very sadly. There is a risk here that is potentially more pervasive, difficult to distinguish, less dramatic, and just as sad. That is the risk that health care professionals will prescribe medications, patients will pay for them and take them as prescribed, the patients will not get better because the medicine is not harmful, it is just ineffective. It may be ineffective because it was stored improperly somewhere along its journeys, or because it is packaged or labeled inappropriately, or because it is a counterfeit drug that is actually a placebo. In any of these cases, it is our job as the lawmakers, the agencies who enforce the laws, and the manufacturers who understand the molecules and the science around the molecules to assure we have the controls in place to prevent this from occurring.

Chart A

U.S. Supply Chain – Current System



Regulated by FDA
Product Approval; Good Manufacturing Practices, Factory Inspections

Regulated by FDA and State Board of Pharmacy
Good Manufacturing Practices, Prescription Drug Marketing Act, Factory Inspections

Regulated by State Board of Pharmacy
Pharmacy Registration, Pharmacy Inspections

Mr. UPTON. I appreciate that very much. And just as I sort of get prepared to ask—I do have a number of questions, but I am going to yield, I think, first to my colleague from Ohio, Mr. Strickland.

Mr. STRICKLAND. Sure. Thank you, Mr. Chairman.

Let me begin by saying that you are a very effective witness. I think you advocate for your thoughts and opinions effectively and some of the things that you have said have given me pause. And so I want to thank you for that.

Having said that, I would like also to share some thoughts with you.

Ms. MEHRINGER. Certainly.

Mr. STRICKLAND. You are a scientist, and that is your responsibility with your industry. I respect that, and I respect the science, and I respect the fact that you spoke to us as you did.

The problem, I think, that has brought this issue forward is the perception, I think, it is based on the fact that the industry that you work for—through no fault of your own certainly—is engaging in practices which cause many of us to think that the American consumer is being treated unfairly; that drugs that are developed, in part, through public resources are available to other citizens and other countries at a cheaper price. And I think there is a perception based on fact that the whole pricing of the pharmaceutical industry is troublesome.

Now, you mentioned a business decision in terms of even going above and beyond what you may be required to do. And that is admirable. Like you, when I buy a medication in this country, I don't worry about its safety. I am glad it is that way.

But I am also troubled by the fact that there is this other issue out there that is driving this concern and this effort, I think. And I think there is an equal responsibility on the part of the industry, just as there is a responsibility on the part of us who sit up here, to try to make sure that both concerns are adequately addressed; that we remain concerned about safety, but we also be concerned for the American consumer, for the senior citizen, for those who maybe can't afford the drugs. And that is a tragedy as well.

And I am so puzzled, in a sense, that the industry would be opposed to a medication benefit under Medicare that would be available to Medicare recipients. I can only assume that the major concern has to do with cost and price and profit. And so I am sitting up here feeling some conflict, because what you say makes a lot of sense to me; but I am also sitting up here thinking, something has got to be done to protect the American consumer.

And so I really don't have a question for you. I just—I will once again state the fact that you said things that make sense to me, and I am going to listen to what you have said and I will try to respond in a way that I think is responsible. But—and you are not responsible for the pricing policies of your industry. But that is the problem, as I see it, that makes many of us look for ways that we can change things for the sake of the American consumer.

So thank you for your testimony.

Ms. MEHRINGER. Thank you.

Mr. UPTON. I thank you for your testimony as well. And the thing that we all struggle with—it certainly came out when we have been totally immersed in the Firestone issue the last couple of weeks.

But one of the points—and I am from Michigan, as you may know—one of the points that I had made was that whenever any of us buy a product—any of our constituents, any American buys a product that is made in America, we have a belief, in fact, that that product is going to be safe; whether it is an automobile, whether it is a tire, whether it is a bottle of Tylenol, it is going to work, it is going to work for the purpose, and that there are regulators at the State and Federal level to, in fact, assure that safety.

As we examined the Firestone issue, one of the items that bothered us the most and became one of the planks in the legislation that is moving here in the House, as well as in the Senate, was that when in fact there was a recall—and there was in Venezuela or Saudi Arabia, and it happened at an earlier time—that that information needed to be passed along to, in this case, NHTSA under the Department of Transportation.

And in fact, in good testimony, the President of Ford, Mr. Nasser, indicated that in the future they would do that; they didn't need a law, they would do that. He called on other members to do that as well. And we will make sure that that is done by getting this legislation passed.

One of the points—and I use that as the example because in the hearing that we had earlier this summer, the FDA indicated, and Dr. Henney reiterated today, that they would require manufacturers to notify the FDA when they receive poor quality material, whether it be directly counterfeit or maybe it was a mistake in the process. And it just—I guess those of us nonchemists—and I presume that my colleague and friend, Mr. Strickland is a non; but it seems to me common sense that when you identify a faulty product coming up the line that somewhere along the line that information is going to be passed along. And based on that, they can begin to trace it.

Maybe, you know, this is a bad character, maybe we have to watch them a little bit closer, maybe we will send those FDA inspectors there every year instead of who knows when. But at least they are going to get in the process, and we are going to weed them out and we are going to build cooperation between industry folks like your company, Eli Lilly, and other good players, whether it be Pharmacia, Upjohn or any other—obviously, the client base. Because it is your folks working on the line, it is your reputation, as you point out, to make sure and ensure that that product is safe from the very beginning of your testimony to the very end. And that even after it leaves your operation, you are going to have the ability to know the quality control as it ends up finally in someone's medicine cabinet when that son, daughter, parents, whoever takes that medication.

But I have to say, as we have begun to look at this process, again the issue of requiring companies to let us know about foreign recalls, the process that you, we would have hoped, I would think had already been part of the process; that in fact when you found that company overseas that put milled sugar in—tainted, you know, 30 percent of the barrels of bulk material that came in; when you found that, there is a red flag—not only would you tell your other industry peers, of which—obviously, you have them, but in fact there would be some type of inspection or some alert to make sure that what the real-life example, what happened in Haiti with the tainted glycerine, would not and could not happen again.

But there was no checklist, though; is that right?

Ms. MEHRINGER. To my knowledge—and I am not an expert in counterfeit, but to my knowledge, there is no formal requirement for that. However, also, to my knowledge, there is a great deal of cooperation between the pharmaceutical industry and the FDA on counterfeiting.

Mr. UPTON. That is in this country. But what about in products that actually come from overseas, where in fact you may not have the inspectors that come in and in fact things are found, whether it is the little example that I used at the end, before I broke for the vote, with the company in India?

Ms. MEHRINGER. I do believe, although not required, there have been meetings between corporate security people and the FDA to discuss these very issues. And I would ask you to consult with the FDA and the OCI on those conversations to my knowledge would have been voluntary. But we clearly have seen that counterfeiting is a real threat and have seen the FDA as our ally there, working against that, even if it didn't originate here.

Mr. UPTON. So you would certainly support the FDA's new initiative to begin to catch that?

Ms. MEHRINGER. Yes.

Mr. UPTON. Now, as I understand also—one of the questions that has bothered me for some time, when I learned it, was that Eli Lilly and other pharmaceutical companies manufactured the same product for different countries, obviously; but why is it that they do them in different colors and different shapes and sizes? I mean, it would seem to me, if you want to trace something, particularly if something is going to go overseas and perhaps come back, which we don't know exactly what is going to happen, that that would be a very easy way to figure out and would help the Customs folks, who have an enormous task in front of them. Why wouldn't there be some—I don't want to call it "policing," but some just standards, or normalcy, repetitive to the products, no matter what it is?

Ms. MEHRINGER. Actually, for the most part, we would welcome that. The underlying issue is that the drug approval process in countries around the world is very fragmented. So certain drugs have been launched in various countries at different times and approvals have been given; and those approvals—in the course of those approvals, each agency seems to want its own labeling or its own small nuance.

Each agency dictates to us what is now approved. We now submit identical submissions in the U.S. and Europe, and we would love for the FDA and Europe both to say, that is fine, just like you submitted them; but then the changes start. And in order to market in that area of the world, we must abide by those changes.

Mr. UPTON. But someone actually says we would rather have them green than blue or yellow?

Ms. MEHRINGER. That is more market driven than regulatorily driven. There are countries that want plain white tablets. That is the standard; that is what they want. They think that is what the customer expects, and so we are——

Mr. UPTON. It must be aspirin, because it is white.

Ms. MEHRINGER. That is right. That is right.

There are other countries, like the U.S., that want unique identifiers, distinct color, shape, size and form.

So speaking for the whole pharmaceutical industry, not everyone has the same appreciation, as the American public does, or the same wants or the same needs.

So, again, these products which have been launched over a period of the last 20 years and have gone through the drug development process, we have at times been focused on pleasing the regulatory agencies and on pleasing the customers. But frankly, it would be much easier for us as manufacturers to make one package, one label, and one presentation. I would welcome that.

You understand, though, that I am not free to change that?

Mr. UPTON. I understand that.

You talked about keeping track of the records, and obviously the company, the manufacturers, keep a record from start to finish, the lots. And do the pharmacies really do that or not? I don't know the answer to the question.

Ms. MEHRINGER. Pharmacies do not track by lot number, no.

Mr. UPTON. So once you ship it out—the wholesalers do, right?

Ms. MEHRINGER. The wholesalers, our own distribution centers do. I do not know that all the wholesalers do. We can track it to the wholesaler level.

Mr. UPTON. But you indicated that—the example that you used, the mother that called you to say, "My daughter has got a problem;" give me 2 hours—you can track it through your system.

Let's say you gave it to ABC wholesaler, who ships it out to Kmart, to use them as an example. Do they all have the records then of that—are you able to—are they able to track it from that? To use a real-life example, when that happens, have they been cooperative and have they been able to have the information that you have really needed to reassure that parent?

Ms. MEHRINGER. When we go to the wholesalers, we have lot number accountability to the wholesalers. The shipment from the wholesalers on to the pharmacies is generally not tracked by lot numbers. But they have been cooperative, absolutely.

It is important to recognize that the law provides for various levels of recalls. And that is dependent upon the risk to safety and the risk to health. If we are in a recall situation, we work with the FDA; we determine, do we need to go to the wholesalers, do we need to go the pharmacies or to the American public? I think the whole system works together and is very cooperative at that point.

Mr. UPTON. That page was for me.

I guess the last question is, we try to assure the absolute quality assurance to the individual. There really isn't any single test that can be used on that product, whether it be coming from Mexico or Canada or China. I mean, there are so many different ways in terms of what a chemist would look for to ascertain the purity of that substance. It is really a very tough test. We were commenting up here, the staff was able to take, I guess you could say, a field trip that was rather lengthy; and they shared some of the information with us in terms of the thousands of pills that come across at particular border crossings virtually every day. And you really can't say it is this; you know, you hope that it is, but there is no real—without a lab, you can't really tell.

Ms. MEHRINGER. You need a very specialized lab; simple chemical testing will not tell you that. In fact, the FDA has established their own forensic testing lab, which is quite a speciality lab, that they can—I believe they call it "fingerprint" products and try to discern if a material is counterfeit or not. That is the only lab in the FDA, I believe, that deals with that because they have those specialized capabilities.

So this is not a matter of routine, let's find a chemist and a third-party lab and take a look at this. It is very specialized to be able to actually fingerprint that drug.

To your point, also the limitations of testing are—testing gives very limited information. It is a single point of what happens. Unfortunately, these molecules are dynamic. They change, they degrade; when they see heat, they see moisture, they degrade a little more. They don't just sit there in the solution, in the injectable vial, waiting for someone to take them.

That, again, is why you must have a knowledge of the molecule. You must have a knowledge of the formulation. You must have a knowledge of those requirements. So if you get a single point of testing someone—it might be 92 percent—someone might think that is good. That may be bad because you know that at the rate of degradation, it is going to be ineffective in a matter of few months.

You have to put the testing in the whole context of the knowledge of the drug.

Mr. UPTON. I know that I can speak for all the members of the subcommittee. We appreciate your time and testimony. We look forward to working with you and hearing from you on this issue in the future.

I don't know—Ted, do you have anything?

Mr. STRICKLAND. Just, I want to thank the witness.

Mr. UPTON. Thank you very much.

[Whereupon, at 1:50 p.m., the subcommittee was adjourned.]

[Additional material submitted for the record follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 11 2000

The Honorable Fred Upton
Chairman, Subcommittee on Oversight
and Investigations
Committee on Commerce
House of Representatives
Washington, D.C. 20515-6116

Dear Mr. Chairman:

This letter is in final response to the Committee's October 3, 2000, hearing on Counterfeit Bulk Drugs. The questions from the Committee are restated, followed by the Food and Drug Administration's (FDA or the Agency) response.

Questions from Mr. Dingell

1. **During a recent meeting with both majority and minority staffs on the drug reimportation proposals, your staff provided a three-page budget document that illustrated the likely costs of these proposals for the FDA. Staff asked for the supporting work papers used to arrive at the many assumptions put together in the three-page document. Staff was told that no work papers exist, and that most of this was done by a "working group." It is curious that an agency embracing legislation that will dramatically increase its workload does not have a detailed set of work papers or other supporting documents to support such analysis. Please provide us with all documentation used to arrive at the budgetary predictions made on the three-page document you provided to the Committee.**

FDA advised Committee staff at that meeting, that we did not have the working papers with us at that time and that we would provide them to the Committee in follow-up to the meeting. It is correct that a working group drawing upon numerous offices within FDA largely developed the budget estimates for implementation of the drug reimportation proposals. Copies of documents used by the working group in developing the budget estimates are enclosed at TAB A. The enclosed information contains confidential information protected from disclosure to the public under the Freedom of Information Act (Title 5, United States Code [USC] § 552), and FDA's regulations. We ask that the Committee not publish these enclosed working papers as part of the hearing record or otherwise make public any information contained in these documents. We would, of course, be glad to discuss with the Committee staff the confidentiality of any specific information.

2. **It is my understanding that the FDA has still not developed a specific frequency target for agency inspections of foreign firms that ship to the U.S. for Good Manufacturing Practices (GMPs). Please explain whether this is the case, and if so, why the FDA has not done so. If it is not the case, please describe the present frequency target FDA uses to inspect foreign firms that make drug products shipped to the U.S.**

In 1997, FDA established a "Strategy for Scheduling Surveillance Inspections for Foreign Drug Manufacturers," as recommended by the Foreign Inspection Work Group. The inspection strategy is referred to as the Tier System, which establishes the current frequency targets for Agency inspections of foreign firms. The Tier system was established because FDA does not have the inspection resources needed to meet a target frequency of every two years for foreign manufacturers, as required for domestic manufacturers.

The Tier System is defined as follows:

Tier I (one-year target) -- Inspection of firms previously classified as Official Action Indicated (OAI).

Tier II (three-year target) -- Inspection of firms manufacturing sterile products.

Tier III (five-year target) -- Inspection of firms:
  a) Having a high number of new drug applications (NDA) or abbreviated new drug applications (ANDA),
  b) Manufacturing Active Pharmaceutical Ingredients (API) for injectable dosage forms, and
  c) Manufacturing finished products (not sterile).

Tier IV (six-year target) -- all other firms.

3. **It is my understanding that many foreign firms that ship drug products to the U.S. have not received a GMP inspection from the FDA in as many as six to eight years, and maybe longer. Because FDA's information technology system(s) still remains in disarray (and has been that way for years), your agency still cannot generate an accurate assessment of precisely (a) what firms currently are shipping to the U.S., (b) when they should have been last inspected, and (c) when they actually were last inspected. Please explain why this is still the case, and describe any public health implications that may result for failure to inspect these manufacturers on regular two-year intervals.**

FDA has acknowledged, both at the two Committee hearings on this matter and in subsequent correspondence that its information technology (IT) systems need to be improved and enhanced. To that end, the Agency has made some progress, as reported by Jane E. Henney, M.D., Commissioner of Food and Drugs, in her testimony at the October 3 hearing.

Specifically, Dr. Henney reported that the Agency would: 1) make the Forensic Chemistry Center (FCC) API database available electronically to all field inspectors by January 2001, and 2) expand the Establishment Evaluation System (EES) pilot project in the Philadelphia District Office nationwide by the end of 2000. In addition, FDA is reviewing an IT needs assessment done by a private contractor.

As stated at the October 3 hearing, the FCC database currently contains information or "fingerprints" on 330 API's that have been collected and chemically analyzed by FCC. This information is one important tool, which FDA can use to more quickly identify whether or not a product is authentic or counterfeit.

Expanding the availability of the EES database, that tracks information related to the approval process for drug applications, to the Agency's import inspectors will allow them to retrieve important additional data in about three to four minutes on any API entry, which increases the probability of confirming authentic sourcing of APIs.

As you know, the Center for Drug Evaluation and Research's (CDER) Office of Compliance utilizes the Foreign Inspection Teams (OCFITS) database as its primary repository of information regarding firms that are actively inspected. This system provides current and reliable data on when foreign firms were inspected since 1994, which is when the system was brought online. CDER also uses the Drug Registration and Listing System to provide information on firms that have listed drugs, as well as the EES database.

Information contained in these databases has been cross-checked with data from the Office of Regulatory Affairs' (ORA) OASIS database to identify a list of firms for which we can not determine an approved dosage form manufacturer in the United States (U.S.), as described in the Agency's written testimony.

On average, FDA accomplishes 225 drug-manufacturing inspections per year, with 160 of those being combined pre-approval and good manufacturing (GMP) inspections. Twenty five (25) are GMP surveillance inspections (which would include firms never inspected or not inspected in over six years), 30 are pre-approval only inspections and five are compliance follow-up inspections.

FDA addresses these firms which require inspection on a surveillance basis and schedules them for coverage each fiscal year. Due to limited resources these firms are scheduled on a priority basis using the risk-based tiered approach described above. CDER identified 100 firms per year for the past two fiscal years for surveillance coverage under the tiered approach, however 75 of 100 were not completed.

The Agency would like to complete more GMP inspections each year, but our current program does identify priorities for coverage using a risk-based approach, which best addresses public health needs within the constraints of our current resources. In addition, while recognizing that testing is no substitute for GMP inspections, it must be noted that the majority of pharmaceutical imports are APIs that are subject to testing and release prior to use by the dosage form manufacturer.

While FDA recognizes the shortcomings of its information systems, we are making the best use of currently available data to prioritize and identify firms for inspectional coverage. We do not have a database specifically designed to contain firms that require GMP inspection. We have developed a regulation pending before the Office of Management and Budget (OMB) which provides for the annual registration of foreign firms. We believe this requirement will be implemented during Fiscal Year (FY) 2001. This requirement is specifically directed at providing a list of foreign firms that require GMP inspection.

4. **As accurately as possible, please provide your present backlog of foreign inspections today as measured against FDA's effort to conduct such inspections on a two-year basis. Please also describe the factors that led to FDA's current backlog.**

As stated above, the Tier System was initiated to make the most effective use of limited resources because FDA has not been able to perform inspections of all foreign firms every two years. However, we have been able to accomplish about 225 foreign GMP inspections each year, the majority of which are driven by pre-approval assignments. Approximately 460 different facilities have been inspected one or more times during fiscal years 1999 and 2000, covering 30 Tier I firms, 80 Tier II firms, 90 Tier III firms and 260 Tier IV firms.

Measured against the Drug Registration and Listing database of approximately 1,900 facilities, we would calculate a potential "backlog" of approximately 1,500 foreign facilities which have not been inspected in the past two years. The Agency has been able to generally meet our inspectional goals with respect to Tier I firms and many Tier II firms, which are the highest priority. Due to the information technology challenges the Agency is currently addressing, we are not readily able to assess the inspectional status of the 1,500 firms. However, we are performing a manual cross-check of these firms with other information sources in order to fully determine the extent of the potential backlog. It is entirely possible that many of these firms, although registered or listed, are not currently shipping product to the U.S. We will be glad to share further information about the status of these firms with the Committee as it is developed.

5. **Please state what resources are needed for FDA to know the internal GMP conditions of all plants shipping drug products to the U.S. Please provide this in both dollar amounts and FTEs, if possible.**

As we reported in our letter of November 28, 2000, based on CDER's drug listing data, we estimate that there are now approximately 1,900 foreign firms that may be offering drugs for entry to the U.S. market. If these firms were inspected every two years (at 950 inspections per year), our annual projected operating costs for inspections, trip planning and evaluation of findings would be approximately $23 million. The table below describes the calculations arriving at this amount.

This represents only a calculation of direct inspection resources. The actual costs to support a sustained program of offshore inspections worldwide would require inspection organization enhancements and personnel management adjustments. For example, currently we accomplish foreign inspections with inspectors based at field offices in U.S. These inspectors are needed to inspect the domestic industry and travel for foreign inspections part-time. A program of two-year foreign inspections would likely require the restructuring of inspector stationing.

PROJECTED ANNUAL INSPECTIONS COST		
Activity	Explanation	Cost
ORA Inspectors	950 inspections x 0.1451 FTE per inspec. = 138FTE 138 FTE x $112,000 FTE cost =	$ 15,456,000
ORA travel planning	10 FTE x $112,000 FTE cost =	1,120,000
Travel	950 inspections x $5,000 per inspection =	4,750,000
CDER review	950 reports x 0.016 FTE per review = 15.2 FTE 15.2 FTE x $112,000 FTE cost =	1,702,400
TOTAL		$ 23,028,400

6. **One of the most significant problems facing FDA's foreign inspection program is that the OASIS system still cannot adequately keep pace with FDA's present workload. It is my understanding that FDA is attempting to upgrade and/or replace much of that system, and has hired an outside contractor for this effort. Please provide (a) the cost of the outside contractor; (b) what this upgrade is expected to cost; and (c) how long the system**

upgrade/replacement will take. Also, I understand that the contractor has already issued cost and other analyses to the FDA. Please provide all such reports.

FDA routinely maintains and upgrades the OASIS system but has no plans to replace that system. However, in response to certain issues raised at the June 8, 2000, hearing on counterfeit APIs, FDA hired an outside contractor to assess the Agency's overall information technology (IT) systems. This contractor evaluated IT systems created and maintained by many Agency components, not just the ORA's Division of Import Operations, which maintains the OASIS system. The focus of this review was to find ways to provide more accurate, complete, and timely information to import inspectors.

The goal is to implement IT solutions that will improve admissibility decisions relative to safety and quality. For instance, the contractor discovered during its assessment that import personnel may have to access up to 17 different databases to gather information necessary to make admissibility decisions. The contractor's proposed solution would make it possible to access all of these data sets through a single password-protected account. The contractor did not evaluate any of the Agency's legacy systems, including OASIS, which is maintained by another outside contractor. The contract cost for this evaluation was $211,196.

The contractor has estimated that various short-term solutions, if implemented, would cost $5.9 million. One of the two long-term proposals is to develop an inventory of all FDA-regulated firms at a developmental cost of $1.3 million. The second proposal deals with the use of countermeasure technologies to detect and deter import violations. This initial study only provided an estimate of $125,000 for 500,000 labels with unique serial numbers and barcodes. The cost of developing a system to support such a measure was not included.

The total long-term IT cost is not firm at this point. The Agency has not completed its evaluation of the report sufficiently to concur in the accuracy of these estimates, and we are assessing what resources may be available to implement the project. A copy of the contractor's report will be made available once FDA's evaluation of the recommendations are completed.

7. **In previous correspondence with this Subcommittee, FDA disclosed that a number of foreign firms were exporting (or have exported) drug-related materials to the U.S., yet have never been inspected by FDA authorities. Now, your testimony states that there are as many as 242 drug manufacturers in 36 countries that appear to have exported to the U.S. in 1999, but have not been inspected. Please provide a list of these firms to the Subcommittee, and what products each has shipped. Also, please provide an analysis of what the potential implications of this finding are on the safety of the Nation's drug supply. Finally, please state specifically what the FDA is now doing about these firms.**

The Agency issued an import alert (IA #66-66)on October 3, 2000, for 242 foreign API manufacturers, in 36 countries, listing the products covered, that appear to have exported to the U.S. in 1999, but have not been inspected, according to the EES database. A copy is enclosed at Tab B. These firms will be prevented from importing the specified APIs into the U.S. unless they can provide documentation that the dosage form manufacturer consignee holds an approval for the use of that API in a finished human drug product or documentation establishing that the API is intended for an authorized use (e.g., for a non-application product).

The final phase of the analysis of the OASIS data will be to identify any firms FDA has not inspected, but which are referenced in approved human and animal drug applications. In some cases, investigations at the domestic firms or consignees are being conducted to determine if APIs from unapproved sources were used to manufacture finished drug products.

8. **Please provide an explanation of whether the FDA now believes that the threat of drug counterfeiting is less today than before the Prescription Drug Marketing Act went into effect.**

As you know, the Prescription Drug Marketing Act (PDMA) was enacted by Congress in 1988 after two years of Congressional investigations and hearings that found widespread diversion of prescription drug samples, import and export abuses involving prescription drugs identified as "American goods returned", and diversion of retail prescription stock through the secondary wholesaler network.

The law's enactment recognized that the diversion of prescription drugs presented serious public health safety issues, i.e., counterfeit, subpotent, adulterated, and misbranded drugs were being funneled into the national distribution system by distributors whose only concern was how cheaply they could obtain the drugs, not their source or quality.

The Agency has made no formal assessment of the extent to which PDMA may have thwarted such behavior. It should be noted that since the passage of PDMA, the technology used for counterfeiting has continued to evolve and the market for prescription drugs has increased. It is possible that the disincentives for counterfeiting enacted under the PDMA may be offset to some degree by the incentives provided by technology and market potential.

The PDMA extended the Federal Food, Drug and Cosmetic Act into areas not previously regulated by FDA, and gave the Agency new authorities, including the ability to pursue civil and criminal fines. FDA has developed a continuing partnership with other Federal law enforcement agencies in investigating possible violations of the PDMA.

Enforcement of the PDMA includes investigation into possible violations, recommendation and implementation of regulatory actions, litigation support, preparation of advisory opinions, and informal guidance to the regulated industry, health care professionals, other Federal, State, and local drug regulatory agencies, and consumers. CDER also maintains the industry reports mandated by the PDMA, and additional reports concerning possible PDMA related drug diversion.

From December 1992 through September 2000, FDA's Office of Criminal Investigations (OCI) has opened a total of 422 cases involving violations of the PDMA. One hundred forty seven (147) of these have been drug sample diversion cases and 275 have been domestic wholesale and/or reimportation drug diversion cases. There have been a total of 479 arrests and 329 convictions as a result of the PDMA cases. Seventy-seven (77) of the arrests and 62 of the convictions are a result of drug sample diversion cases. Four hundred two (402) of those arrests and 267 of the convictions are a result of domestic wholesale and/or reimportation drug diversion cases under the PDMA. Several of these cases were charged as violations of the prohibition on interstate transport of stolen goods or goods obtained by fraud (18 USC 2314).

Based on the additional authorities made available to FDA under the PDMA and the criminal case data cited above, the PDMA has undoubtedly had a significant impact on the ability or willingness of potential counterfeiters to attempt such illegal behavior.

9. On a recent trip to China to investigate issues relating to both FDA foreign inspections and pharmaceutical counterfeiting, Commerce Committee staff were told by several security officials that counterfeit material is often mixed into shipments of legitimate products, as an additional tactic to elude regulators. Thus, rather than entire shipments being counterfeit, in some cases only a part of a total shipment may be illegitimate.

(a) Does FDA believe that such a tactic might be used by counterfeiters today? Has the agency ever seen evidence of this method? If so, please describe the details.

The scenario of mixing counterfeit material with pharmaceuticals from an FDA-approved facility is possible. Information was previously provided to the Commerce Committee on an occurrence based on this scenario reported by the Therapeutic Goods Administration of Australia. FDA has not directly encountered evidence of such an incident.

(b) Is batch testing, which the proposed legislation has as the primary test of authenticity, a reliable method for protecting the U.S. consumers from potentially rogue and dangerous counterfeit drugs?

Quality testing of each batch of bulk drugs would provide some valuable information on potency, purity, and other specifications. A counterfeit bulk drug, however, might also meet these specifications and such testing could not be relied upon to detect certain counterfeit products.

(c) If a batch test were only to test the legitimate product contained in a mixed shipment, how, under this legislation, will counterfeit material be detected? Is there a methodology for doing this?

A program that includes chemical fingerprint testing and evaluation of labeling, containers, seals, certificates of analysis, shipping records and covert markings will be more useful in detecting and deterring shipments of counterfeit bulk drugs. It is not possible at this time to determine the statistical probability of detecting counterfeit drugs using these samples and analytical techniques.

(d) FDA has long told this Committee that quality assurance cannot be "tested" into a system (hence, the purpose behind the current foreign inspection program), which is why the agency has rejected batch testing as a final test for finished product and bulk materials sent to the U.S. Do you believe that batch testing is suitable to meet the same stringent safety requirements long relied upon by the agency?

Batch testing of bulk materials would provide some information on the quality of a sample taken from the material. The sample could not be guaranteed to represent the entire batch or shipment. Typical analyses might include identity, potency (purity), impurities (total or individual), pH, heavy metals, etc. Depending on the number of batches involved and the complexity of the tests, this type of batch testing by FDA could be extremely expensive. Additional tests may be indicated by the specific product or specifications, or by observations made during an inspection. For instance, a firm may be producing or misusing pesticides, or producing penicillin in the same facilities. These would be significant problems, which would not be detected through routine batch testing.

We do not believe batch testing is a suitable substitute for a GMP inspection which provides a more comprehensive evaluation of a manufacturer's facilities, equipment, written procedures, training, controls, testing, labeling, and quality control and quality assurance. These GMPs must be observed in operation to evaluate a firm's compliance.

10. Why doesn't the FDA simply batch test raw ingredients as they come into the U.S. instead of relying an expensive GMP inspections?

Testing is less effective than inspections because:

- Tests are specific for what they are designed to detect. Other contaminants or even filth may be undetected;
- Tests only provide information about the specimen tested;
- The amount of a lot tested is minute compared to the untested portion of the lot sold and used;
- It is much easier to manipulate test samples than manufacturing systems; and
- Tests are done after manufacture necessitating waste if results are out of specification.

The question implies that testing may be an inexpensive regulatory operation compared to "expensive GMP inspections." Testing requires sophisticated laboratories, inventories of reagents and equipment, sample collection, well-trained analysts, libraries of up-to-date methods, operating procedures, OSHA/EPA compliance, etc. It is questionable whether this approach is in fact less expensive than site inspections.

GMPs cover the actual manufacture and testing of drug products that consumers will receive. Testing of bulk raw material (assuming that this term refers to the refined active ingredient in bulk form rather than a bulk chemical) is insufficient for ensuring the safety and efficacy of a finished dosage form product.

11. **The PDMA and its implementing regulations established standards for storage and handling of medicines as they move from a manufacturer to a retail pharmacy. These provisions were enacted because pharmaceuticals are very sensitive to various environmental factors, and therefore drugs are packaged under controlled conditions. Storage of pharmaceuticals under extreme environments can, as you know, lead to premature deterioration of the drug. The new legislation's testing requirements for product degradation will provide information on drug potency at the point a test is conducted (and not across the shelf life of the drug). This means there is no guarantee that a product imported from another country will arrive with roughly the same shelf life as envisioned by the manufacturer. If drug products have been subjected to temperature extremes while being shipped or stored, or are improperly repackaged, the medicines could not be guaranteed to meet its specifications up to the**

expiration date. Moreover, imported drugs will require repackaging and relabeling so that the imported product conforms with an FDA-approved and required dosage form, packaging and product labeling for the American market. This means there is a very real chance that an American patient will unknowingly receive pharmaceuticals that are not fully efficacious because of premature loss of potency. Do you agree with this assessment, and if so, how can these very real and potentially dangerous possibilities be dealt with in the implementation of the new legislation?

FDA is concerned about the issues raised under the scenario you describe. That is why the Agency supported provisions of the Medicine Equity and Drug Safety Act of 2000 such as those which provide that the testing of incoming finished dosage form, approved prescription drugs will include forensic identity and stability profile testing. Further, FDA's wholesaler licensing regulation, which applies to all distributors of prescription drugs in the U.S., including manufacturers, requires all such drugs to be stored appropriately (in accordance with requirements for labeling, USP requirements, and under controlled room temperatures).

It should also be noted that under the statutory pedigree provision, the traceability of a prescription drug product from the original manufacturer throughout the wholesale distribution system up to the retail customer will be possible. Traceability enhances the ability to determine compliance with wholesale licensing storage and handling requirements.

12. **As you know, in the United States, pharmaceutical recalls are initiated by manufacturers because a manufacturer can quickly and efficiently locate its products through its wholesale distribution system. Under the new legislation, imported drug manufacturers may not have a systematic way of knowing where a drug originated, or even if a product has been transshipped to multiple countries before entering the United States. It not only allows a drug to be shipped through multiple foreign locations, but also for a drug to be transferred among any number of intermediaries. Because of the likelihood of repackaging, it is not even certain that the product will be labeled with the original manufacturers lot**

number. How can a manufacturer's recall be administered efficiently and effectively under these new conditions?

Again, FDA is concerned about the issues you raise. FDA does not believe, however, that the Medicine Equity and Drug Safety Act of 2000 eliminates the ability of regulatory authorities, including FDA, to trace backward from a recalling firm to the ultimate manufacturer or, more importantly, the firm that caused the recalling defect (not always the manufacturer).

Each recalling firm using Title 21, Code of Federal Regulations § 7 guidelines notifies their own consignees of the recall and normally instructs them to notify their consignees of the recall, so that the notification process works in a timely way down the chain from the recalling firm to the end users, or consumers. In some cases the recalling firm requests the sub-accounts to give them their list of consignees in order that they directly notify the end users.

In the United States, FDA performs facility inspections in order to work backward from the recalling firm to the firm responsible for the violation or defect under recall. This is accomplished by a review of manufacturing, repackaging, and distribution records required to be kept by the pharmaceutical industry under the FD&C Act and implementing regulations for current good manufacturing practices (CGMPs) (21 CFR §210 and 211). These records enable the Agency to trace a product even if one or more firms have changed its labeling and lot numbers. Foreign firms who manufacture drugs under FDA approval also maintain these type of records for review by FDA.

13. If in the future we see many new repackaging facilities play a role in bringing products to the U.S. market, do you have any concerns regarding these facilities?

Yes, anytime another party is added to the process, concerns are raised about maintaining the integrity of the system.

However, the repackaging of drug products imported into the U.S. should not be a problem because U.S. repackagers are subject to the GMP regulations, including provisions for packaging and labeling, testing and storage of drug products. FDA conducts routine inspections of repackagers to assess their compliance with the GMP regulations.

Repackaging facilities, as manufacturers under the FD&C Act, are required to register and drug list, meet GMPs, and adhere to wholesaler licensing regulations.

14. It appears that certain products are inherently difficult to repackage or re-label, such as sterile injection solutions, auto injectors, ointments, and pre-filled syringes, What are the issues relating to repackaging such products, and what are FDA's concerns regarding any new legislation that allows for relabeling and repackaging?

FDA would consider any manipulation of any sterile product to be a manufacturing operation that would be subject to application submission and GMP inspection. We believe the repackaging of such products (sterile injection solutions, auto injectors, ointments, and pre-filled syringes) which entails actual product manipulation may not be feasible due to the difficulties in maintaining sterility in attempting to perform such manipulation. Relabeling and repackaging of intact containers of some products may be feasible only if it can be done in a manner where new labels can be applied to the exteriors of the packing, older labels can be readily removed and the product is not manipulated in any way compromising sterility.

15. What percentage of the bulk raw material used to manufacture drugs globally is considered substandard or even adulterated?

FDA is not aware of any estimates of the amount of substandard or adulterated bulk raw material used worldwide. It has been estimated by the World Health Organization (WHO) that up to ten percent of the APIs used worldwide are counterfeit, with that number as high as 50 to 70 percent in some developing countries.

16. Which countries are the most problematic when it comes to selling substandard or counterfeit bulk ingredients, or does FDA even have such an assessment?

17. Which countries are the most problematic when it comes to selling substandard or counterfeit finished products? Does FDA have such an assessment?

FDA is not aware of such an assessment regarding countries, which are the most problematic for selling substandard or counterfeit bulk ingredients or finished products.

FDA is not aware of data on which countries have the highest risk for exporting counterfeit or substandard bulk drugs to the U.S. We do have data on which countries had the highest Official Action Indicated (OAI) rate for GMP inspections from 1994 to 2000. The five countries of those having 50 or more inspections during that period were:

Country	Number of Inspections	Number OAI	Percentage OAI
China	68	16	24%
Switzerland	82	16	20%
Canada	126	18	14%
United Kingdom	147	17	12%
India	57	7	12%

18. At the June 8th hearing, we discussed that there is no requirement that a U.S. manufacturer discovering counterfeit material in the manufacturing of a finished product must immediately report the problem to the FDA. FDA told us that it was exploring whether it could require this through regulation. Please provide us with a status report on this matter.

FDA has determined that it has the authority to require this information by regulation, and has begun drafting a regulation.

Questions from Mr. Coburn

1. Why did the FDA choose to approve RU 486 without any patient protections, specifically requiring the drug to only be allowed to be administered by a physician who has appropriate experience dealing with the complications of an abortion?

Under the authority of 21 CFR 314, Subpart H, FDA has restricted the use of the drug to physicians who can accurately determine the duration of a woman's pregnancy and detect an ectopic pregnancy. Physicians who prescribe mifepristone must also be able to provide surgical intervention in cases of incomplete expulsion or severe bleeding, or they must have made plans in advance to provide such care through others.

In addition, the Agency has added the following patient protections:

- Prior to using the drug, a woman must first read the Medication Guide and sign a Patient Agreement Form confirming that she understands what side effects can occur and that she is committed to proceeding with the treatment.
- After reading the guide and signing the agreement form, treatment involves three visits to a physician. On the first visit, the patient receives a dose of mifepristone. On the second visit, on day three, the patient returns to have the physician determine if expulsion has occurred. If expulsion has not occurred, the patent receives misoprostol. Approximately 14 days after taking mifepristone, the patient must return for a follow-up visit to confirm that termination has occurred.
- The drug will not be available through pharmacies or legally available over the Internet.
- Postmarket surveillance studies to monitor safety.

2. By approving RU-486, the FDA has actually approved two drugs as part of a combination. The second drug, Cytotec, was thereby approved for an off label use.

(a) Is this legal?

Under the approved treatment regimen, misoprostol is administered on day three to help stimulate uterine contractions. The use of misoprostol is contained in the approved labeling of mifepristone. It is based on the clinical trials for the regimen (treatment program) of the two drugs, which FDA found to be safe and effective for the termination of early pregnancy.

(b) Has the FDA ever before approved a drug for a use not intended by the manufacturer?

There are a number of examples of drugs and devices that have been approved as safe and effective in combination with another drug or device for a use that was not sought by the sponsor of the second product.

- Persantine tablets were approved for use in conjunction with warfarin for prevention of thromboembolic events following cardiac valve replacement. The sponsor of Warfarin did not seek this indication at the time.
- Coronary stents were approved for use in percutaneous transluminal coronary angioplasty (PTCA) in conjunction with several drugs including ticlopidine, clopidogrel, heparin, and warfarin. The sponsors of these drugs did not seek approval for PTCA at the time.

(c) Has the FDA ever before endorsed or promoted the off-label use of a drug after it has expressed, in collaboration with the drug's producer, its disapproval of that off-label use?

The Agency does not endorse or promote the use of any drug. FDA makes approval decisions based on science, adhering strictly to its legal mandate and mission as a science-based public health regulatory agency.

Currently, Cytotec (misoprostol) is approved for use in the prevention of nonsteroidal anti-inflammatory drug (NSAID)-induced gastritis. In addition, mifepristone is approved for use with misoprostol for medical termination of early pregnancy. When using misoprostol for the prevention of NSAID-induced gastritis, patients should be warned that it may cause miscarriage. Patients who want to remain pregnant should not use misoprostol to treat NSAID-induced gastritis. When used correctly, misoprostol in combination with mifepristone is safe and effective for the termination of early pregnancy.

3. **When Cytotec is used in conjunction with mifepristone to complete a chemical abortion by causing a woman's cervix to dilate and expel a fetus, does Cytotec induce labor or abortion?**

Mifepristone and misoprostol are administered sequentially as a regimen to induce medical abortion by terminating pregnancies of 49 days or less. Mifepristone blocks a hormone called progesterone that is needed for pregnancy to continue. If expulsion has not taken place by day three, misoprostol is administered to help stimulate uterine contractions. In a small percentage of cases, expulsion will occur prior to misoprostol administration.

4. Did the FDA use Cytotec in clinical trials with mifepristone?

FDA did not conduct clinical trials with mifepristone. The sponsor of the mifepristone NDA conducted the clinical trials. Cytotec, a brand of misoprostol, was used in those trials.

5. Does the FDA believe that Cytotec will be used as the second drug in the two-drug regimen to chemically induce abortion?

Misoprostol is the second drug used in the two-drug treatment program to induce medical abortion by terminating pregnancies of 49 days or less. Cytotec is a brand of misoprostol and can be used as part of the regimen.

6. Does the FDA believe that the health of women will be endangered if Cytotec is not used in conjunction with mifepristone to expel an expired fetus from a woman's womb?

FDA has not reached any conclusions on the safety and effectiveness of what you suggest, because there is little data on the use of mifepristone alone, without the use of an accompanying prostaglandin such as Cytotec.

However, in a small percentage of cases (e.g., 6 percent in the U.S. trials; 5.3 percent in the French trials), expulsion occurs without the use of misoprostol. If expulsion has not taken place by day three, misoprostol is administered to help stimulate uterine contractions.

7. Please describe in detail other situations in which the FDA has contradicted the advice contained in drug warning letters posted on its web site and explain its reasons for doing so.

FDA is not contradicting the advice contained in warning letters posted on its web site. When using misoprostol for the prevention of NSAID-induced gastritis, physicians and patients should heed the warnings, which explain that the drug may cause miscarriage. A woman who is or may become pregnant -- and who does not wish to terminate her pregnancy -- should not take misoprostol for prevention of gastric ulcers or any other reason. As part of the mifepristone-misoprostol regimen, misoprostol is appropriate for use to terminate early pregnancy.

Thank you again for making this a part of the public record. If you have further questions, please let us know.

Sincerely,

Melinda K. Plaisier
Associate Commissioner
for Legislation

cc: The Honorable Ron Klink
Ranking Minority Member
Subcommittee on Oversight
and Investigations

Enclosures

IA #66-66 - 10/3/00, IMPORT ALERT #66-66, "DETENTION WITHOUT PHYSICAL EXAMINATION OF APIs THAT APPEAR TO BE MISBRANDED UNDER 502(f)(1) BECAUSE THEY DO NOT MEET THE REQUIREMENTS FOR THE LABELING EXEMPTIONS IN 21 CFR 201.122" ATTACHMENT 11/7/00

TYPE OF ALERT: Detention Without Physical Examination (DWPE)

(Note: This import alert represents the Agency's current guidance to FDA field personnel regarding the manufacturer(s) and/or product(s) at issue. It does not create or confer any rights for or on any person, and does not operate to bind FDA or the public).

PRODUCT: Active Pharmaceutical Ingredients (APIs)

PRODUCT CODE:

GPI = DR (drugs) with PIC = [][][][]S[][]
GPI = AB (antibiotics) with PIC = [][][][]S[][]

PROBLEM: Misbranded drugs

PAF: LBL - Labeling

PAC FOR COLLECTION: 52002

COUNTRY: See attachment

MANUFACTURER/ SHIPPER FEI#: See attachment

IMPORTER'S ID#: N/A

OASIS CHARGE CODE: DIRECTIONS

CHARGE: "The article is subject to refusal of admission pursuant to section 801(a)(3) in that it appears to be misbranded in that it lacks adequate directions for its intended use. [Misbranding, Section 502(f)(1)]."

NOTE: Under 502(f)(1), an API must have labeling that lists adequate directions for its use unless the API is subject to exemptions from labeling found in 201.122.

RECOMMENDING OFFICE: DIOP (HFC-170)

REASON FOR ALERT: OASIS records indicate that a large volume of bulk chemicals which can be used as APIs in human medicines that require NDAs, ANDAs, or INDs are being offered for entry into the U.S.

NDA - Imported APIs labeled for further manufacturing and processing or labeled as chemical substances are frequently destined for pharmaceutical processors that formulate finished drug products. These drug substances, consigned to individuals or processors who formulate and distribute human drugs, may be misbranded under Section 502(f)(1).

IND - Sponsors of investigational new drug applications frequently import from foreign countries either the dosage form or the API for use in laboratory research or clinical trials.

Some persons importing APIs have found that they could obtain entry of these articles if they simply supply an NDA or IND number at the point of entry. Districts should be alert to the possibility that: 1) the NDA or IND number provided does not cover the source of the particular API or 2) the persons importing the API have no authorization to refer to the particular NDA or IND number. In the past, the persons importing an API have referred to legitimate numbers to get their APIs released, but the APIs were not destined for use in the application referenced.

CDER and ORA are in the process of making the Establishment Evaluation System (EES) available to the field. When available, field offices should utilize EES to search and verify the status of an API, its manufacturer, whether it has been referenced in a valid NDA or whether it is the subject of a valid IND. Districts that do not have access to EES should contact Joseph E. Tracey, DIOP, 301-443-6553 to verify this status.

(OASIS entry records can be compared to CDER records for NDAs, ANDAs, and IND exemptions to verify the source and status of an API.)

EXEMPTION UNDER 21 CFR 201.122

API labeling invariably lacks adequate directions for use as required by Section 502(f)(1) of the Act. However, such drugs may be subject to an exemption under 21 CFR subpart 201.122. This regulation requires specific labeling on the package when adequate directions for use are missing, such as "Caution: For manufacturing, processing, or repacking."

However, the exemption under 21 CFR 201.122 will not apply to a substance intended for a use in the manufacture, processing, or repacking of the API which causes the finished article to be a new drug, unless:

A. an approved NDA covers the production and delivery of the API to the application holder by persons named in the application; or

B. if no application is approved with respect to the API, the label statement "Caution: For manufacturing, processing, or repacking" is immediately supplemented by the words "in the preparation of a new drug or new animal drug limited by Federal law to investigational use," and the delivery is made for use only in the manufacture of such new drug or new animal drug limited to investigational use as provided in 21 CFR part 312 or part 511.1.

The API/manufacturer combinations listed in Attachment A appear to represent importations of APIs to be used for the manufacture, processing, or repacking of drugs which the Act and regulations require to be the subject of an approved NDA or a valid IND. However, either the person receiving the API or the person importing the API appears not to meet the statutory and/or regulatory requirements regarding labeling. Further, it appears that the Agency has never inspected the declared manufacturer's GMPs for that imported API.

GUIDANCE: Detain without physical examination the APIs from the manufacturers named in the attachment to this Import Alert.

Districts may detain without physical examination APIs from the persons listed in Attachment A because it appears that the API is misbranded based on its lack of adequate directions for use as required by section 502(f)(1) of the Act and its failure to meet the requirements of the exemption found in 201.122. Persons importing these APIs may obtain release of the detained articles if these persons can supply evidence establishing that the article is:

1. intended for pharmacy compounding that meets the requirements of section 503Aof the Act, including that the API:

    a. is accompanied by a valid certificate of analysis,

    b. is manufactured by an establishment registered under section 510 of the Act, and

    c. does not appear on a list of drugs identified in 21 CFR 216.24, that have been withdrawn or removed from the market for reasons of safety or effectiveness.

2. intended for use in the manufacture, processing, or repacking of an over-the-counter product or prescription product that does not require an NDA; or

3. a new animal drug, or intended for use in the manufacture, processing, or repacking of a new animal drug, subject to an NADA;

and, therefore, the API is not subject to this import alert.

OR

Persons importing APIs may obtain release of the detained articles by supplying evidence establishing that the article is:

1. intended for use in the manufacture, processing, or repacking of a human drug that is itself the subject of an approved NDA, and that the API is from the appropriate source; or
2. it is covered by IND requirements at 21 CFR 312.110(a).

For questions or issues concerning science, science policy, sample collection, analysis, preparation, or analytical methodology, contact the Division of Field Science at (301) 827-7605.

This guidance is not intended to address new animal drugs or investigational new animal drugs addressed by Import Alert number 68-09. If the imported APIs are intended for use in an NADA or INAD, refer to Import Alert number 68-09.

If the APIs are intended for the compounding of finished drugs by pharmacies, persons importing the APIs must comply with the requirements in 503A of the FDCA.

This guidance does not apply to excipients or APIs intended for use in OTC drugs or prescription drugs that do not require a new drug application.

PRIORITIZATION GUIDANCE: N/A

FOI: No purging is required.

KEYWORDS: NDA, IND, New Drugs, Bulk Drugs

PREPARED BY: Ted Poplawski, DIOP, 301-443-6553

DATE LOADED INTO FIARS: OCTOBER 3, 2000

ATTACHMENT FOR IMPORT ALERT# 66-66

Firms and API's recommended for DWPE

AUSTRALIA (AU)

FIRM	PRODUCT/ PRODUCT CODE
Institute Of Drug Technology 45 Wadhurst Drive Boronia, Ausrtalia FEI# 3000219354	Minocycline HCl/56E[]S61 11/2/00

AUSTRIA (AT)

FIRM	PRODUCT/ PRODUCT CODE
Biochemie Gmbh Biochemiestrabe 10 Kundl (Tyrol), Austria FEI# 3001034356	Kanamycin Sulfate/56D[]S31 11/2/00 Rifampicin/56K[]S70 11/2/00

BAHAMAS (BS)

FIRM	PRODUCT/ PRODUCT CODE
Allied Signal P.O. Box F-42430 W. Sunrise Highway Freeport, Bahamas FEI# 3002584993	Naproxen/62G[]S49 11/2/00
Pharmaceutical Fine Chemicals Ltd. P.O. Box F-2430 Freeport, Bahamas FEI# 3001369302	Doxazosin Mesylate/62O[]S27 11/2/00
Syntex Pharmaceuticals P.O. Box 2430 Freeport, Bahamas FEI# 1000163107	Butoconozole Nitrate/61W[]S56 11/2/00 Flunisolide/64L[]S26 11/2/00

BELGIUM (BE)

FIRM	PRODUCT/ PRODUCT CODE
Acros Organics N.V. Janseen Pharmaceuticalaan 34 Geel, Belgium FEI# 3001268405	Oxytetracycline HCl/56E[]S67 11/2/00
Alcon Couvreur Nv	Brinzolamide/66R[]S08

Rijksweg 14 B-2870 Puurs, Belgium FEI# 3002808051	11/2/00
Omnichem N.V. Industrial Research Park Louvain, Belgium FEI#	Vinblastine Sulfate/62I[]S66 11/2/00
Pfizer Service Co. SA Hoge Wei 10 Zaventem, Belgium FEI# 1000232385	Doxazosin Mesylate/62O[]S27 11/2/00

CANADA (CA)

Acic Fine Chemicals Inc. 6501 B Mississauga Road Mississauga, Canada FEI# 3000142731	Cephalexin/56C[]S73 11/2/00
Brantford Chemicals Inc. 42-46 Spalding Drive Brantford, Canada FEI# 3000114091	Buspirone HCl/66M[]S09 11/2/00 Fluvoxamine Maleate/61N[]S67 11/2/00
Brantford Chemicals Inc. Station Main P.O. Box 1976 Brantford, Canada FEI# 1000610334	Buspirone HCl/66M[]S09 11/2/00 Fluvoxamine Maleate/61N[]S67 11/2/00
Bulk Pharmaceuticals Ltd. 465 Milner Avenue #4 Scarborough, Canada FEI# 3001158880	Tetracycline HCl/56E[]S81 11/2/00
Choisy Laboratories Ltd. 390 Blvd St`Laurent Est Louiseville, Canada FEI# 7978	Penicillin/56A[]S10,56A[]S20, 56A[]S99, 56B[]S99 11/2/00
Draxis Pharma 16751 Trans Canada Highway Kirkland, Canada FEI# 3002528120	Apomorphine/64C[]S01 11/2/00 Trifluridine/62V[]S40 11/2/00
Forchem Canada Ltd. 235 Yorkland Blvd., Suite 300 Toronto, Canada FEI# 3002625441	Clindamycin Phosphate/ 56J[]S22, 56J[]S31 11/2/00
Formulex Canada Inc. 5950 EST Chemin Cote De Liesse Blvd. Ville Mont Royal, Canada FEI# 3002269313	Piroxicam/62G[]S59 11/2/00
Intergen Biomanufacturing Corp. 55 Glen Scarlett Road Toronto, Canada FEI# 3000172241	Insulin (Bovine)/61P[]S36 11/2/00
Patheon Inc. 2100 Syntex Court On	Synalar/55Q[][]22, 53L[][]07 11/2/00

Mississauga, Canada FEI# 3000264888	
Rtp Pharma Inc. 810 Chemin Du Golf Verdun, Canada FEI# 3001342164	Cyclosporine/62G[]S89 11/2/00
Schering Corporation, Ltd. 3535 Trans Canada Highway Pointe Claire, Canada FEI# 1582	Progesterone/65J[]S31 11/2/00
The Upjohn Company 865 York Mills Rd. Don Mills, Canada FEI# 1000408737	Antibiotics N.E.C./56Y[]S99 11/2/00
Wyeth & Ayerst 1765 Cote Vertu Bldg #14 St. Laurent, Canada FEI# 1000206786	Gonadorelin/64M[]S03 11/2/00
Wyeth-Ayerst Canada Inc. 1025 Blvd Marcel Laurin St. Laurent, Canada FEI# 3000986282	Rapamycin/64T[][]99 11/2/00

CHINA, PEOPLE'S REPUBLIC OF (CN)

FIRM	PRODUCT/PRODUCT CODE
Anhui Meheco Heparin Factory 361 Jixi Road Anhui, China FEI# 3002651373	Sodium Heparin/ 61L[]S08 10/10/00
Chengdu Mechem Medicines & Chemicals Co. 22 Jingsi Street Chengdu, China FEI# 3001049983	Oxytetracycline/ 56E[]S65 10/10/00
China Export Bases Development Corp. No# 1 Jianghan Road Chengdu, China FEI# 1000201375	Gentamicin/56D[]S20 Oxytetracycline/56E[]S65 Streptomycin/56D[]S70 10/10/00
China Hunam Walion Imp & Exp Corp. 153 Wu Yu Road (E) Changsha, China FEI# 3002723729	Sodium Heparin/ 61L[]S08 10/10/00
China Jiangsu Medicines 2156 North Zhong Road Nanjing, China FEI# 1000174806	Testosterone/ 60N[]S14 10/10/00
China National 129 Henan Road	Prednisone/ 64L[]S50

Tianjin, China FEI# 3002743488	10/10/00
China National Light Industrial Products Import & Export Cor No. 32 Qixian North Street Tiexi Shenyang, China FEI# 1000357908	Trimethoprim/ 61H[]S03 10/10/00
Dandong Pharmaceutical Factory Dandong City Liaoning, China FEI# 3002674128	Promethazine/ 61T[]S17 10/10/00
He Nan Yong Qi Chemicals Co. Ltd. East Tenmin Road, Tang Yin County Henan Province, China FEI# 3002811052	Diclofenac Sodium/ 62G[]S18 10/10/00
Henan Lihua Pharmaceutical Co Ltd. N. Antang Rd. Henan, China FEI# 3000312540	Prednisone/ 64L[]S50 10/10/00
Huaiyin Wellkong Bioeng 3 West Beijing Road Huaiyin, China FEI# 3002738533	Sodium Heparin/ 61L[]S08 10/10/00
Huashu Pharmaceutical Corporation Northern Tangu Street Shijiazhung, China FEI# 3000714293	Oxytetracycline/ 56E[]S65 10/10/00
Huazhong Pharmaceuticals Co. Wensheng Center Wenjin Public Tian Bei 1 Shenzhen, China FEI# 3000683585	Progesterone/ 65J[]S31 10/10/00
Hubei Zenith Airbeck Pharmaceutical Co. 46 Xianshan Road Xiangfan City, China FEI# 3002699141	Progesterone/ 65J[]S31 10/10/00
Hubei Zenith Airbeck Pharmaceutical 46 Xianshan Road Hubei, China FEI# 3003085185	Progesterone/ 65J[]S31 10/10/00
Jiangsu Yabang Group Co. Niutang Bridge Changzhou City Jiangsu, China FEI# 3002161348	Albendazole/ 60W[]S01 10/10/00
Jiangsu Sainty International G Unknown Street Jiangsu, China FEI# 3002705146	Flucytosine/ 61W[]S10 10/10/00
Lukang Pharmaceutical 173 West Tajbai Road Shandong, China FEI# 3002664271	Streptomycin/ 56D[]S70 10/10/00

Machinex Ninbo Ltd. 68 Mayuan Road Ningbo, China FEI# 3002397898	Oxytetracycline/ 56E[]S65 10/10/00
Nanhai Beisha Medical Material Factory Nanhai Branch Guangdong,China FEI# 3000315903	Sulfamethazine/ 61G[]S55 10/10/00
Nanjing Chemicals Import & Export Corporation, Ltd. 281 Jiankang Road Nanjing, China FEI# 1000466898	Triazolam/ 65V[]S41 10/10/00
Nanjing Machinery 255 Shanzhong Rd. Nanjing, China FEI# 1000607425	Sucralfate/60S[]S26 10/10/00
Sanming Pharmeceuticals Factory 46 Taijiang Road Fujian, China FEI# 3000270002	Gentamicin/ 56D[]S20 10/10/00
Shandong Foreign Trade Corpora 51 Taiping Rd. Qingdao, China FEI# 1000535663	Lincomycin/ 56J[]S99 10/10/00
Shandong Ju County Foreign Trade Canned 11 Nannai Rd. Qingdao, China FEI# 1000422523	Kanamycin/ 56D[]S30 10/10/00
Shanghai Buddy International Trading Co. Room F 26 Floor A Building Shanghai, China FEI# 3002997245	Progesterone/ 65J[]S31 10/10/00
Shanghai Exceed Dragon Intl. Trade Corp. 205 Chong Qing Road North Shanghai, China FEI# 3001550665	Tetracycline/56E[]S80 Dihydrostreptomycin/ 56D[]S10 10/10/00
Shanghai Kj Import & Export Corp. No. 139 Dong Yuan Yi Cun Room 1006 Shanghai, China FEI# 1000404710	Gentamycin/56D[]S20 10/10/00
Shanghai K J No. 6 Pharmaceuticals 1290 Shanghai, China FEI# 3000448987	Gentamycin/56D[]S20 10/10/00
Shanghai Medicines & Health Products 21 Zhongshan Road, 3rd flr Shanghai, China FEI# 1000315530	Kanamycin/56D[]S30 10/10/00
Shanghai Sun Tar Audio Products Manufacturing Co., Ltd. No. 50 Yuc Chia Wan Lung Hua Xilu	Sulfadiazine/ 61G[]S47 10/10/00

Shanghai, China FEI# 1000273817	
Shanghai Worldbest Industry 211 Shangcheng Lu Shanghai, China FEI# 3002624436	Procaine HCl/ 60Q[]S46 10/10/00
Shijiazhuang Pharmaceutical Factory 58 Zhongshan Road Shijiazhuang, China FEI# 1000316479	Oxytetracycline/ 56E[]S65 10/10/00
Sichuan Yibin Foreign Economic Dev Buliding No 3 Minzhu Road Yibin City, China FEI# 3002288333	Oxytetracycline/ 56E[]S65 10/10/00
Sinochem Zhuhai Co.Ltd. Bldg.18 Fl#11 Lian Hua Yuan Zhuhai, China FEI# 3001431009	Procaine HCl/ 60Q[]S46 10/10/00
Sinochem Jiangsu Changzuou Import & Export Corporation 5 Peace North Rd., Labour Union Blde. Changzhou, China FEI# 1000437226	Oxacillin Sodium/ 56B[]S55 Adrenocortical Steroid/ 60D[]S99 10/10/00
Sinocrem Bebei Imporrt & Export Corp. 448 Veping Rd. Shijuazhuang, China FEI# 3002485683	Tetracycline/ 56E[]S80 10/10/00
Star Lake Co. Inc. No. 67 Gongnong Road No. Guangdong, China FEI# 3002998736	Ribavirin/ 62V[]S12 10/10/00
Suzhou No 1 Garment Factory Sufu Highway Suzhou, China FEI# 1000646769	Lincomycin/ 56J[]S99 10/10/00
Tianjin Medicines & Health Products Imp & Exp.Corp. 164, Jie Fang Road Tianjin, China FEI# 1000164404	Methocarbamol/ 65Q[]S22 10/10/00
Wujin Jianhu Silk Printing Mill Jian Hu Xiang,Wu Jin Xian, Chang Chang Zhou, China FEI# 3002548649	Progesterone/ 65J[]S31 10/10/00
Wuxi Foreign Trade Zhong Shan Rd, Foreign Bldg. Wuxi, China FEI# 1000455187	Phenylbutazone/ 62Q[]S07 10/10/00
Yancheng Suhui Pharma Co., Ltd. 92 E Jiankang Road Jiangsu, China	Doxycycline/ 56E[]S20 10/10/00

FEI# 3002394098

Yang Zhou Pharmeutical Factory Unknown Jiangsu, China FEI# 3002625526	Teroxalene HCl/ 62R[]S09 10/10/00
Yangpu Zhongxin Chemical Imp. & Exp. Co. Ltd Rm 1505-1508 Unit 1,Hongguan Bldg. Haikou City, China FEI# 3001226841	Progesterone/ 65J[]S31 10/10/00
Zhejiang Medicines & Heal 7 Tian Mu Shan Road Hangzhou, China FEI# 1000344761	Doxorubicin HCl/56H[]S24 Daunorubicin HCl/56H[]S25 Mitomycin/56H[]S45 10/10/00

CROATIA (HR)

Pliva Dd. Zagreb Vukovarska Av 49 Zagreb, Croatia FEI#	Mesalazine/60L[]S85 11/2/00
Pliva-Kalinovicaszetonedjeljska 2 41431 Szeta Nedjelja, Croatia FEI# 3002112548	Atovaquone/62L[]S44 11/2/00

DENMARK (DK)

Dumex Alpharma P.O. 1736 Copenhagen, Denmark FEI# 3000302730	Colistin/56F[]S21 11/2/00 Colistin Methanesulfate/56F[]S21 11/2/00 Colistin sulfate/56F[]S21 11/2/00
Dumex Alpharma Dalslandsgade 11 Copenhagen, Denmark FEI# 3002710222	Colistin/56F[]S21 11/2/00 Colistin Methanesulfate/56F[]S21 11/2/00 Colistin sulfate/56F[]S21 11/2/00
Marsing And Co. Agenavej 18 18 Greve, Denmark FEI# 3002701552	Penicillin G Procaine/ 56A[]S10 11/2/00
Polypeptide Laboratories As Fredericksberggade 1 Copenhagen, Denmark FEI# 1000575924	Vasopressin/64R[]S16 11/2/00

FINLAND (FI)

Fermion Orion 65	Buspirone HCl/66M[]S09 11/2/00

Espoo, Finland FEI# 1000446360	
Orion Corporation 65 Espoo, Finland FEI# 1000176807	6-Mercaptopurine/62I[]S30 11/2/00 Tamoxifen Citrate/61U[]S05 11/2/00
Orion Corporation Ltd.(Fermion) 28 P.O. Box Espoo, Finland FEI# 1000316345	Buspirone HCl/66M[]S09 11/2/00

FRANCE (FR)

Claro Fra 70 Par, France FEI# 3001558577	Allantoin/65L[]S99 11/2/00
Conseil Europe 3133 Rue De Calais Strasbourg Cedex, France FEI# 3001833087	Oxybutynin/61K[]S34 11/2/00
Conseil De L'Europe Ave De L'Europe Strasbourg, France FEI# 1000328317	Famotidine/60S[]S22 11/2/00 Felodipine/62O[]S32 11/2/00 Kanamycin Monosulphate/ 56D[]S31 11/2/00 Prednisolone/64L[]S50 11/2/00 Vancomycin/56K[]S85 11/2/00
Dolisos Laboratoires 71 Rue Beaubourg Paris, France FEI# 1000254716	Somatotropine/64R[]S99 11/2/00
Finorga 8 Route De Givors Chasse Sur Rhone, France FEI# 412	Brinzolamide/66R[]S08 11/2/00
Francopia 82 Ave. Raspail Gentilly, France FEI# 1000561456	Naloxone HCl/60T[]S14 11/2/00
Hoechst Marion Roussel 102 Route De Noisy Romainville, France FEI# 3001109514	Clomiphene Citrate/64M[]S01 11/2/00 Fluorometholone/64L[]S31 11/2/00 Levonogeestrel/64G[]S29 11/2/00 L-Corbadrine HCl/60C[]S42 11/2/00 Pentoxifylline/66S[]S49 11/2/00
Isochem, S.A.	Flavoxate HCl/65Q[]S41

4, Ave. Philippe Lebon Gennevilliers, France FEI# 1496	11/2/00
Merck Sa 6-9 Rue Anquetil Nogent-Sur-Marne, France FEI# 3002527973	Thiothixene/66M[]S62 11/2/00
Merck Sharp & Dohme-Chibret 3 Avenue Hoche Paris, France FEI# 1000360120	Imipenem/64U[]S04 11/2/00
Orsymonde Sa (Ste) 19 R Francois 1er Paris 8e, France FEI# 3002726365	Modafinil/61N[]S74 11/2/00
San Chi 15 Sis, France FEI# 3001311362	Ticlopidine/63E[]S29 11/2/00
Seloc France 19 Rte De Neulan Limay France FEI# 3001382610	Desipramine HCl/61N[]S18 11/2/00
Sipsy 79 Route De Beaucouze Avrille, France FEI# 1438	Cidofovir/62V[]S21 11/2/00
Synthelabo Groupe 22 Avenue Galilee Les Plessis Robinson, France FEI# 1000439227	Betaxolol HCl/62O[]S17 11/2/00 Zolpidem Tartrate/65V[]S56 11/2/00
Synthelabo Groupe Bp 165zone Idustrial D Amilly Montargis Cedex, France FEI# 3002420086	Betaxolol HCl/62O[]S17 11/2/00 Zolpidem Tartrate/65V[]S56 11/2/00

GERMANY (DE)

Boehringer Ingelheim Binger Strasse 173 6507 Ingelheim Frankfurt, Germany FEI# 1000603905	Mexiletine HCl/63E[]S25 11/2/00 Crotamiton/65T[]S02 11/2/00 Camptothecine/62I[]S99 11/2/00
Boehringer Ingelheim Mainzer Strabe 152 Rhein, Germany FEI# 1000255859	Mexiletine HCl/63E[]S25 11/2/00 Crotamiton/65T[]S02 11/2/00 Camptothecine/62I[]S99 11/2/00
Boehringer Ingelheim Int'l. Singer Strasse 73 Ingelheim, Germany	Anisotropine Methylbromide/61K[]S02 11/2/00

FEI# 1000228430	Crotamiton/65T[]S02 11/2/00 Methscopolamine Bromide/61K[]S31 11/2/00 Mexiletine HCl/63E[]S25 11/2/00
Chemische Fabrik Berg Gmbh Altenaer Str 23 Ludenscheid, Germany FEI# 1000314405	Butabarbitol/65V[]S06
Chemische Fabrik Buddenheim Am Rhein 6 Budenheim, Germany FEI# 1000204572	Butabarbitol/65V[]S06 11/2/00
Cyanamid Gmbh Pfaffenrieder Strabe 7 Wolfratshausen, Germnay FEI# 1394	Calcium Leucovorin/61C[]S01 11/2/00
Dangschat Aubenhandelsgesellschaft Gmbh Frankenstrasse 35 Hamburg, Germany FEI# 1000209030	Clotrimazole/61W[]S04 11/2/00
Dr. Gerhard Mann Chem Pharm. Fabrik Gmbh Brunsbutteler Damm 165-173 Berlin, Germany FEI# 1000211017	Timolol Maleate/60X[]S23 11/2/00
Far High Trading Gmbh Speckmannstr 1 D-2239 Hamburg, Germany FEI# 3002399862	Tetracycline/56E[]S80 11/2/00
Galenus Mannheim Sandhofer Strass 116 Mannheim, Germany FEI# 3002609726	Digoxin/63F[]S06 11/2/00 Metaxalone/65Q[]S21 11/2/00 Methyldopa/62C[]S39 11/2/00
Germapharm Spaldingstrabe 210/212 Hamburg, Germany FEI# 1000507194	Clocortolone Pivalate/ 64L[]S11 11/2/00
Haupt Pharma Gmbh Pfaffenrieder Str 5 Wolfratshausen, Germany FEI# 3000310230	Calcium Leucovorin/61C[]S01 11/2/00
Helm Ag Nordkanalstrasse 28 Hamburg, Germany FEI# 3002677363	Gentamycine Sulphate/56D[]S21 11/2/00 Nystatin/56G[]S50 11/2/00 Sulphathiazole/61H[]S09, 61H[]S10 11/2/00

	Tetrahydrozoline HCl/60C[]S51 11/2/00
Heumann Pharma Gmbh Heideloffstrabe 1828 Nurnberg, Germany FEI# 1000355348	Bisoprolol Hemi-fumarate/62O[]S18 11/2/00 Bupivacaine HCl/60Q[]S79 11/2/00
Heumann Pharma Gmbh Nurnberger Strasse 12 Feucht, Germany FEI# 3000242652	Bisoprolol Hemi-fumarate/62O[]S18 11/2/00 Bupivacaine HCl/60Q[]S79 11/2/00
I.I.C.H. Intern. Isotopes Clearing Obergasse 4 Volxheim, Germany FEI# 3002701171	Doxorubicin/56H[]S24 11/2/00
Knoll Ag Postfach 210805 Ludwigshafen-Frankfurt, Germany FEI# 1350	Paroxetine HCl/61N[]S77 11/2/00 Terazosin HCl/62O[]S10 11/2/00
Lederle Arzneimittel Schleebrueggenkamp 15 Munster, Germany FEI# 3002647597	Calcium Leucovorin/61C[]S01 11/2/00
Carl Padberg Zentrifugenbau 7630 Lahr/Schwarzwald Geroldsecker Vorstadt, Germany FEI# 3002774486	Pantoprazol/60S[]S99 11/2/00
Pharma Waldhof Postfach 11-07-32 Dusseldorf, Germany FEI# 1000178978	Idoxuridine/62V[]S08 11/2/00
Pharma Waldhof Gmbh Werk Mannheim/ Auslieferungslager Mannheim, Germany FEI# 1000442761	Idoxuridine/62V[]S08 11/2/00
Roche Diagnostics Sandhoferstrasse 116 Mannheim, Germany FEI# 3002806559	Amitriptyline HCl/61N[]S03 11/2/00 Metaxalone/65Q[]S21 11/2/00
Roche Diagnostics Strabe 16 Mannheim, Germany FEI# 3002776288	Amitriptyline HCl/61N[]S03 11/2/00 Metaxalone/65Q[]S21 11/2/00
Siemsgluss & Sohn P.O. Box 501427 Hamburg, Germany FEI# 1000246499	Gentamycin Sulfate/56D[]S21 11/2/00
Trans Medica Buschstrasse 12 Hamburg, Germany	Penicillin G Potassium/ 56A[]S10, 56A[]S99 11/2/00

FEI# 1000378498

HONG KONG (HK)

FIRM	PORDUCT/PRODUCT CODE
Hovione International Limited Gpo Box 9383 Hong Kong, Hong Kong FEI #1000332708	Doxycline/56E[]S20 11/2/00
Meritor Trading Co., Room 1109 Wellborne Commercial Centre 8 Hong Kong, Hong Kong FEI #3002574858	Neomycin/ 56D[]S40 10/10/00 Neomycin Sulfate/56D[]S41 11/2/00
New Chemic Ltd. Rm. 601 Wing On Plaza 62 Mody Road, Tsimshatsui East Kowloon, Hong Kong FEI #1000207273	Oxytetracycline/56E[]S65 Linycomycin/56J[]S99 Ketoprofen/62G[]S46 Penicillin G Natural/56A[]S10 10/10/00 Penicillin G/56A[]S99 11/2/00

HUNGARY (HU)

FIRM	PORDUCT/PRODUCT CODE
Biogal Pharmaceuticals Pallagi Ut. 13 Debrecen, Hungary FEI# 1276	Mupirocin/61G[]S81 11/2/00
Egis Pharmaceuticals Kereszturi Ut 30-38 Budapest, Hungary FEI# 1279	Tamoxifen Citrate/61U[]S05 11/2/00
Expedition Warehouse If Gedeib Richter Budapest Ex Gyomroi Ut Budapest, Hungary FEI# 3002682437	Mifepristone/65J[]S38 11/2/00
Gedeon Richter P.O.B.1475 Budapest, Hungary FEI# 1000194717	Famotidine/60S[]S22 11/2/00
Gedeon Richter Chemical Works Of Gyomro Gyomroi Ut 19/21 Budapest, Hungary FEI# 1243	Famotidine/60S[]S22 11/2/00

Gedeon Richter Ltd Unknown Street Budapest, Hungary FEI# 3002575623	Dihydroelymoclavine/ 62J[]S99 11/2/00
Icn Hungaryngary Company Limited 4440 Tiszavasvari, Kabay Janos U 29 Budapest, Hungary FEI# 3002366874	Buspirone HCL/66M[]S09 11/2/00

INDIA (IN)

PRODUCT/ FIRM	PRODUCT CODE
Aarti Drugs Industries Ltd 74 Matru Smruti Road No. 4 Mumbai, India FEI #1000382858	Tolnaftate/61W[]S31 10/10/00
Aarti Drugs Limited Mahendra Industria No. 29 Sion Mumbai, India FEI #3001611965	Tolnaftate/61W[]S31 10/10/00
Aarti Drugs Ltd. Plot Nr 109-D, Road 29,, 3rd Flr. Mahendra Ind. Estate Mumbai, India FEI# 1000257863	Tolnaftate 61W[]S31 10/3/00
Ambalal Sarabhai Enterprises Ltd. P.O. Box 31 Wadi Wadi, India FEI# 3002631457	Amphotericin B 56G[]S04 10/3/00
Avik Pharmaceuticals Ltd. 194 Arvind Chambers Bombay, India FEI# 3002771134	Clobetasol Propionate 64L[]S67 10/3/00
Bombay Drug House Private Limited Akurli Road, Kandivli (East) Mumbai, India FEI# 1000190193	Albuterol Sulfate 63B[]S02 10/3/00
Fine Chemicals 89 Princess Street Bombay, India FEI# 3001717561	Piperazine 60W[]S26 10/3/00
Hetero Drugs Limited 8-3-166/5b Ii Floor Deccan Chambers, Erragadda Hyderabad, India FEI# 3000126720	Doxazosin Mesylate 62O[]S27 10/3/00
Lake Chemicals 12 Plain Road Bangalore, India	Lorazepam 66M[]S86 10/3/00

FEI# 3002467300

Medicorp Technologies India Ltd.
86 Sarojini Road
Secunderabad, India
FEI# 3001362853

Acyclovir
62V[]S18
10/3/00

Suven Pharmaceuticals Ltd.
Flat No 205 Brinilaya Estate
Ameerpet, India
FEI# 3001417298

Theophylline
63B[]S30
10/3/00

Synthokem Labs
P.B. No. 1911, Sanathnagar
Hyderabad, India
FEI# 1000184677

Methocarbamol
65Q[]S22
10/3/00

Synthoken Labs Provate Limited
B-5 Industrial Estate
Hyerabad, India
FEI #3002716561

Methocarbamol/65Q[]S22
10/10/00

Tender Remedies
43 Dr V B Gandhi Marc
Mumbai, India
FEI# 3001587063

Metformin HCL
61P[]S55
10/3/00

INDONESIA (ID)

P.T. Aneka Chemic Pintu Besi
33 Jakarta
Pusat, Indonesia
FEI #3002419393

Medrosyprogesterone
ACE/65J[]S21
11/2/00

IRELAND (IE)

Clonmel Healthcare Ltd.
Clonmel Co
Tipperary, Ireland
FEI# 1000187576

Minocycline/56E[]S60
11/2/00

Cranford Ireland Ltd.
20 Clanwilliams Terrace
Dublin, Ireland
FEI# 3002720284

Nystatin/56G[]S50
11/2/00

Eli Lillu Sa
Dunderrow Kinsale
Cork, Ireland
FEI# 1000415014

Fluoxetine/61N[]S29
11/2/00

Iropharm Limited
Vale Road
Wicklow, Ireland
FEI# 1000417222

Diethycarbamazine
Citrate/60W[]S12
11/2/00
Promethazine HCl/61T[]S17
11/2/00

Iropharm Ltd. Vale Road Wicklow, Ireland FEI# 599	Diethycarbamazine Citrate/60W[]S12 11/2/00
Omj Manufacturing Ltd. 3, Wilton Place Dublin, Ireland FEI# 3002668722	Risperidone/66N[]S04 11/2/00
Plaistow Limited Unknown Cork County, Ireland FEI# 10837	Levobunolol/60X[]S26 11/2/00
Sandilands Limited 14/15 Parliament Street, 1st Floor Dublin, Ireland FEI# 3000145069	Trazadone HCL/61N[]S60 11/2/00
Swords Laboratorias Waterly Lane Dublin, Ireland FEI# 1000276442	Etoposide Phosphate/62I[]S78 11/2/00
Syntex Ireland, Ltd. Clarecastle (Ennis) County Clare, Ireland FEI# 1199	Ketorolac Tromethamine/ 62G[]S94 11/2/00

ISRAEL (IL)

Assia BPC/Div. TEVA Group 2 Denmark St. P.O. Box 3190 Petach-Tikva, Israel FEI# 3002806405	Lorazepam/62K[]S05 11/2/00
Chemagis Ltd 3 Hashlosha St. Tel Aviv, Israel FEI# 1000210130	Tramadol/60L[]S69 11/2/00
Chemagis Ltd PO Box 9091 Tel Aviv, Israel FEI# 1000552800	Tramadol/60L[]S69 11/2/00
Sigma Israel Chemicals Ltd P.O. Box 6570 Jerusalem, Israel FEI# 1000289125	Dactinomycin/56H[]S20 11/2/00

ITALY (IT)

Angelini Aprilia S P A	Metaxalone/65[]S21

Via Guardapasso 8 Aprilia, Italy FEI# 1000260820	11/2/00 Trazadone HCl/61N[]S60 11/2/00
Angelini Francesco Acraf Spa Viale Amelia 70, 00181 Rome, Italy FEI# 1000399573	Trazadone HCl/61N[]S60 11/2/00
Archimica S.P.A. Vialo Europa 5 Origgio, Italy FEI# 1000330416	Minocycline HCL/56E[]S61 11/2/00
Cosma Spa Via Colleoni 15/17 Ciserano, Italy FEI# 3000136285	Propranolol HCl/63E[]S13 11/2/00 Tolazamide/61E[]S28 11/2/00
Cs33 Fine Chemicals 33 Corso Sempione Milan, Italy FEI# 3000313809	Amodiaquin HCl/62L[]S23 11/2/00 Budesonide/61E[]S04 11/2/00 Bupivacaine HCl/60Q[]S79 11/2/00 Fluocinolone Acetonide/ 64L[]S27 11/2/00 Hydroxyzine HCl/66M[]S83 11/2/00 Methylprednisolone Acetate/ 64[]S45 11/2/00 Metopropolol Tartrate/62O[]S44 11/2/00 Metronidazole/62L[]S40 11/2/00 Nystatin/56G[]S50 11/2/00 Rivavirin/62V[]S12 11/2/00
Dibra S.P.A Via Per Ceriano Laghetto Ceriano Laghetto (Mi), Italy FEI# 1000171506	Cystogra D/63X[]S43 Cystografin/63X[]S43 11/2/00
Dinamite Dipharma Spa Ss 13 Pontebbana 13 103 Basiliano, Italy FEI# 1000411202	Doxepin/61N[]S24 11/2/00 Tolazamide/61P[]S28 11/2/00
Dinamite Dipharma Spa (Dipharma) Via Bissone N. 5 Baranzate Di Bollate, Italy FEI# 3001624853	Doxepin/61N[]S24 11/2/00 Tolazamide/61P[]S28 11/2/00
Erregierre S.P.A. Via Francesco Baracca 19-57 San Paolo D Argon, Italy FEI# 3002806924	Oxaprozin/62G[]S54 11/2/00 Propafenone HCl/63E[]S28 11/2/00

Fabrica Italy Sintetici S.P.A. Viale Milano,26, Alte Di Montecchio, Italy FEI# 3002806961	Carbamazepine/60L[]S14 11/2/00 Oxazepam/66M[]S91 11/2/00
Farchemia S.R.L. L21 Via Bergamo Treviglio, Italy FEI# 3000181424	Mesalamine/60L[]S85 11/2/00 Oxaprozin/62G[]S54 11/2/00
Farchemia Srl Via Gieveeca Bergamo, Italy FEI# 3002793325	Mesalamine/60L[]S85 11/2/00 Oxaprozin/62G[]S54 11/2/00
Farmabios Via Don Motti 45 Pavia, Italy FEI# 3002806965	Budesonide/61E[]S04 11/2/00 Fluocinolone Acetonide/ 64L[]S27 11/2/00
Gruppo Lepetit 1868 Di Fondazione Milano, Italy FEI# 1000205303	Rifampicin/56K[]S70 11/2/00
Gruppo Lepetit Spa Via R. Lepetit 8 Lainate, Italy FEI# 1000337384	Rifampicin/56K[]S70 11/2/00
Gruppo Lepetit Spa Unknown Brindisi, Italy FEI# 1108	Rifampicin/56K[]S70 11/2/00
Indena Spa Ortles 12 Milan,Italy FEI# 1000448569	Colchicine/66F[]S05 11/2/00 Reserpine/62O[]S06,62C[]S51 11/2/00
Industri Chimiche Farmaceutiche 33045 Nimis (Udine) Udine, Italy FEI# 3002691151	Nifedipine/66S[]S27 11/2/00
Laboratori Mag Spa Viale Gran Sasso 31 Milano, Italy FEI# 1000315026	Clidinium Bromide/61K[]S13 11/2/00 Fluoxetine/61N[]S29 11/2/00
Laboratorio Chimico Internazionale Via Salvini 10 Milan, Italy FEI# 1000292646	Diclofenac Sodium/62G[]S18 11/2/00
Laporte Organics Spa 23 Via Origgio Caronno Italy FEI# 1000442012	Tolbutamide/61P[]S29 11/2/00
Lusochimica S.P.A.	Diltiazem HCl/62O[]S24

Via Carnia 2 Milano, Italy FEI# 1000199592	11/2/00
Mediolast Spa Via Montenapoleone 9 Milano, Italy FEI# 1000262107	Mefloquine HCl/62L[]S49 11/2/00
Pfc Italy Via Tiraboschi 48 Bergamo, Italy FEI# 3001608797	Naproxen Acid/62G[]S49 11/2/00
Pfc Italy Srl Strada Statale Briantea K 36 Bulciago, Italy FEI# 3001419030	Naproxen/62G[]S49 11/2/00 Carbidopa/64U[]S01 11/2/00 Methyldopa/62C[]S38 11/2/00 Verapamil HCl/62O[]S13 11/2/00 Naproxen Sodium/62G[]S50 11/2/00
Pharmacia E Upjohn Spa Via Robert Koch 1 2 Milano, Italy FEI# 3002894707	Glipizide/61P[]S09 11/2/00
Pro Spa Box 249 Cam, Italy FEI# 3000983580	Hydralazine HCl/62C[]S30 11/2/00
Procos S.P.A. Via Leonardo Da Vinci, 3 Cameri, Italy FEI# 10758	Orphenadrine Citrate/65Q[]S24 11/2/00 Phenelzine Sulfate/61N[]S48 11/2/00
Profarmaco (Nobel) Srl Via Cuchiarri 17 Milano, Italy FEI# 1000458419	Chlordiazepoxide/66M[]S76 11/2/00 Flurazepam/64S[]S10 11/2/00 Midazolam/60P[]S03 11/2/00 Oxazepam/66M[]S91 11/2/00
Promek Srl Via Isonzo 17 Milano, Italy FEI# 1000366812	Flurazepam/64S[]S10 11/2/00 Oxazepam/66M[]S91 11/2/00
Prosintex Industrie Chimiche Italiane S.P.A. Via Enrico Fermi 20/26 Settimo Milanese, Italy FEI# 3002807245	Atenolol/60X[]S17 11/2/00 Labetalol HCL/62O[]S39 11/2/00 Metoprolol Tartrate/62O[]S44 11/2/00 Terazosin HCl/62O[]S10 11/2/00
Sicor S.P.A	Epirubicin HCl/62Z[]S03

(Societa Italy Corticosteroidi) Via Terrazzano, 77 Rho (Milan), Italy FEI# 3002808174	11/2/00
Societa Italy Medicinali Scandicci Loc. Montanino Al Filarone 125 Reggello, Italy FEI# 1000225479	Bupivacaine HCl/60Q[]S79 11/2/00
Societa Italy Medicinali Scandicci P.O. Box 390 Firenze, Italy FEI# 1000249538	Bupivacaine HCl/60Q[]S79 11/2/00
Societa Italy Medicinali Scandicci "Via F.G. Angelico, 34 Firenze, Italy FEI# 1000179464	Bupivacaine HCl/60Q[]S79 11/2/00
Solchem Italy S.P.A. Via Della Victoria Mulazzano, Italy FEI# 3002808211	Oxandrolone/60N[]S09 11/2/00 Oxaprozin/62G[]S54 11/2/00
Trifarma Srl V G. Guarini Matteucci 1 Milano Mi, Italy FEI# 1000285520	Perphenazine/66M[]S49 11/2/00
Vis Farmaceutici S.P.S. Viale Delle Industria 54-56 Padova, Italy FEI# 3002808449	Imiprimine/61N[]S32 11/2/00
Westwood Intrafin S.A. Neuhofstrasso 6 Baar, Italy FEI# 1000531100	Cefadroxil Monohydrate/ 61F[]S53 11/2/00 Cefepime/56C[]S53 11/2/00 Ampicillin Sodium/56B[]S09 11/2/00 Cefazolin/56C[]S11 11/2/00
Zambon Group Spa Via Lillo Del Duca 10 Bresso, Italy FEI# 1000280098	Nifedipine Micronized/66S[]S27 11/2/00

JAPAN (JP)

Ajinomoto Co Ltd 1-5-8 Kyobashi 1-Chome Chuo-Ku Tokyo, Japan	L-Dopa/62J[]S09 11/2/00

FEI# 1000140570

Akebono Corporation No.1-12-13 Nihonbashi-Muromachi Tokyo, Japan FEI# 1000195063	Clemastine Fumarate/61X[]S10 11/2/00
Boehringer Ingelheim Kanda Center Bldg 2-3-2 Tokyo, Japan FEI #1000567268	Mexiletine HCl/63E[]S25 11/2/00 Crotamiton/65T[]S02 11/2/00 Camptothecine/62I[]S99 11/2/00
Fujiisawa Pharmaceutical Co., Ltd. 4-7, Doshomachi 3-Chome Osaka, Japan FEI# 1000164970	Vancomycin HCl/56K[]S85 11/2/00
Jung Corp 5-12 Nihonbashi Tokyo, Japan FEI# 1000534008	Doxorubicin HCL/56H[]S24 11/2/00
MSD (Japan) Co., Ltd. Kowa Bldg. No.16 Annex, 9-20 Tokyo, Japan FEI# 1000182400	Levadopa/62J[]S09 11/2/00
Mitsubishi Corp. 6-3 Marunouchi 2-Chome Tokyo, Japan FEI# 1000109842	Clemastine Fumarate/ 61X[]S10 11/2/00
Mitsubishi Corp. 3-1 Marunouchi 2-Chome Chiyoda-Ku Tokyo, Japan FEI #1000190487	Clemastine Fumarate/61X[][]10 11/2/00
Moriya Sangyo K.K. 6-6-3 Shinjuku Kokusai Bldg, FEI# 3001624159	Somatropin/64R[]S21 11/2/00 Shinjuku Tokyo, J
Otsuka Chemical Co.,Ltd. 3-2-27 Ote-Dori Chou-Ku Osaka, Japan FEI# 1000176995	Tazobactam/56Y[]S99 11/2/00 Agent for Schizophrenia/ 65A[]S99 11/2/00 Mucosta/66V[][]99 11/2/00 OPC-14597 - Agent/65A[]S99 11/2/00
Otsuka Pharmaceutical Co Ltd 224-18 Aza Ebisuno Tokushima, Japan FEI #1000228008	Agent for Schizophrenia/ 65A[]S99 11/2/00 Mucosta/66V[][]99 11/2/00 OPC-14597 - Agent/65A[]S99 11/2/00

Tokuyama Corp 2 3 5 Higashi Gotanda Tokyo, Japan FEI# 3002594273	Propantheline Bromide/ 61K[]S44 11/2/00
Tokuyama Corporation 4-5 Nishi Shinbashi Tokyo, Japan FEI# 3002696762	Propantheline/61K[]S44 11/2/00 Propantheline Bromide/ 61K[]S44 11/2/00
Yamanouchi International Ltd. 3-11,2-Chome, Nihonbashi-Honcho Tokyo, Japan FEI# 1000381676	Chloroxazone/65O[]S31 11/2/00

KOREA, REPUBLIC OF (KR)

Chong Kun Dang Corp. 410, Sintorim-Dong, Yong Dungpo-Ku Seoul, Korea FEI# 934	Demeclocyclene/56E[]S15 11/2/00 Lovastatin/62B[]S99, 61J[]S12 11/2/00
Lg Chemical Ltd 1041 Moonji-Dong Taejon, Korea FEI #3001578355	Fluoroquinolone/61H[]S99 11/2/00
Lg Chemical Ltd 20th - 27th Floors, The Lg Twin Towers, Seoul, Korea FEI #1000489126	Fluoroquinolone/61H[]S99 11/2/00
Yuhan Co. 49-6 Tae Bang Dong Seoul, Korea FEI# 3002535348	Pyrazineamide/61H[]S27 11/2/00

LUXEMBOURG (LU)

Archid S.A. 13 Ryc De Bertholet Manno, Luxembourg FEI# 3002542707	Fluvoxamine Maleate/ 61N[]S67 11/2/00

MEXICO (MX)

Helm De Mexico Proton No 2 Col. Naucalpan Estado De Mexico, Mexico FEI# 3002095391	Prednisolone/64L[]S50, 64L[]S52, 64L[]S56 11/2/00
Sintenovo S.A. De C.V. Call 4 No. 26 Mexico City, Mexico FEI# 3002757763	Phenylbutazone/62Q[]S07 11/2/00
Syntex, S.A. Km 4, Carretera Cuernavaca-Cuautla Cuernavaca, Mexico	Ethinyl Estradiol/64G[]S19 11/2/00

FEI# 894

NETHERLANDS (NL)

Dsm Anti Infectives P.O. Box 1 Delft, Netherlands FEI# 3002757967	Erythromycin/56I[]S10, 56I[]S20, 56I[]S25 11/2/00
Industrial Pharmaceutical Products Division P.O. Box 1 Ma Delft, Netherlands FEI# 3002680063	Nystatin/56G[]S50 11/2/00

PANAMA (PA)

Syntex Pharmaceuticals Int'L Limited P.O. Box 7386 Panama, Panama FEI# 1000574157	Ketorolac Tromethamine/62G[]S94 11/2/00

PHILIPPINES (PI)

Searle (Phillipine) Inc. No. 29 Edsa City Of Mandaluyong, Philippines FEI# 3002784880	Metronidazole/62L[]S40 11/2/00

POLAND (PL)

Pharmaceutical Works Polfa Ul.Pelpinska 19 Starogard Gdanski, Poland FEI# 1000216620	Acxetazolamide/63D[]S01 11/2/00

PORTUGAL (PT)

Hovione International Limited 8 Travessa Do Ferreiro Lisboa, Portugal FEI# 1000378108	Beclomethasone/64L[]S02 11/2/00 Betamethasone/64L[]S03, 64L[]S06, 64L[]S08 11/2/00

SINGAPORE (SG)

Fisons Pte Limited 61 Gul Circle Singapore FEI# 1000414917	Nedocromil Sodium/61E[]S10 11/2/00
Schering-Plough Ltd. 50 Tuas West Drive Singapore FEI# 3001572888	Abetalol HCl/62O[]S39 11/2/00

SOUTH AFRICA (ZA)

Fine Chemicals 15 Hawkins Ave. Epping, South Africa FEI# 796	Thiothixene/66M[]S62, 66M[]S63 11/2/00 Vinblastine Sulphate/62I[]S66

11/2/00
Vincritine Sulphate/62I[]S67
11/2/00

SPAIN (ES)

Chemferm Industrial Pharmaceuticals Poligono Ind. Urvasa Barcelona, Spain FEI# 3002806741	Cephalexin Monohydrate/ 56C[]S27 11/2/00 Cephalexin Monohydrate/ 56C[]S27 11/2/00
Chemo Iberica SA Gran Via Carlos 7 98 Barcelona, Spain FEI# 1000174729	Acebutolol HCl/60X[]S15 11/2/00 Acyclovir/62V[]S18 11/2/00 Ciprofloxacin/61F[]S54, 61F[]S55 11/2/00 Omeprazole/62K[]S10 11/2/00 Ranitidine HCl/60S[]S25 11/2/00
Esteve Quimica S.A. Avda. Mare De Deu´ De Montserrat 12 Barcelona, Spain FEI# 1000194139	Felopidine/62O[]S32 11/2/00 Lisinopril/62C[]S65, 62O[]S40 11/2/00 Loratidine/61E[]S08 11/2/00 Nabumetone/62G[]S97 11/2/00 Omeprazole/62K[]S10 11/2/00 Quinapril/62O[]S04 11/2/00
Farmhispania S.A. 1 Mayo S/N Barcelona Spain, FEI# 1000427568	Lisinopril/62C[]S65, 62O[]S40 11/2/00
Farmhispania S.A. 25 De Mayo Barcelona, Spain FEI# 3002728105	Lisinopril/62C[]S65, 62O[]S40 11/2/00
Fermentaciones Y Sintesis Espanolas,S.A. Costello 23 Madrid, Spain FEI# 1000180159	Famotidine/62V[]S05 11/2/00
Gmb Industrias Gmb Sa Virgill 24 Barcelona Spain FEI# 1000553741	Sulfapyridine/66F[]S02 11/2/00
Medichem S.A. Travesera De Gracia 92 Barcelona, Spain FEI# 3000144561	Etodolic Acid/62G[]S24 11/2/00 Felodipine/62O[]S32 11/2/00

	Fluvoxamine Maleate/61N[]S67 11/2/00
Medichem Sa Avda Diagonal 513 Barcelona, Spain FEI# 3001624850	Etodolic Acid/62G[]S24 11/2/00 Felodipine/62O[]S32 11/2/00 Fluvoxamine Maleate/61N[]S67 11/2/00
Quimica Sintetica, SA Calle Dulcinea Alcala De Henares, Madrid, Spain FEI# 3002807965	Famitidine/60S[]S22 11/2/00 Famotine HCl/62V[]S05 11/2/00 Fluoxetine HCl/61N[]S29 11/2/00 Ciprofloxacin HCl/61F[]S55 11/2/00

SWEDEN (SE)

Dupont Chemoswed P.O. Box 839 Malmo, Sweden FEI# 3000181361	Warfarin Sodium/61L[]S13 11/02/00
Ethical Pharmaceuticals Sw Ab Lundavagen 151 Malmo, Sweeden FEI#3000094190	Carbidopa Monohydrate/64U[]S01 11/02/00 Levodopa/62J[]S09 11/02/00

SWITZERLAND (CH)

Adechsa Sa P.O. Box 567 Zug, Switzerland FEI# 3002614607	Fluticasone Propionate/63B[]S25 11/02/00 Ranitidine HCL/60T[]S99 11/2/00
Cerbio Pharma Sa Industral Biologics Lugano, Switzerland FEI# 3002749465	Leucovorin Calcium/61C[]S01 11/02/00
Cerbios Pharma Via Plan Scairolo 6 Barbengo, Switzerland FEI# 1000403851	Leucovorin/61C[]S01 11/02/00 Leucovorin Calcium/61C[]S01 11/02/00
Cilag Ag 201 / 209 Hochstrasse Schaffhausen, Switzerland FEI# 3001631676	Econazole Nitrate/61W[]S44 11/02/00 Mefloquine HCl/62L[]S30 11/02/00 Methimazole/66K[]S01 11/02/00
Cilag Ag	Econazole Nitrate/61W[]S44

Hochstrasse 201 Schaffhausen, Switzerland FEI# 3002315816	11/02/00 Mefloquine HCl/62L[]S30 11/02/00 Methimazole/66K[]S01 11/02/00
Cilag Ag Hochstrasse 210 Schaffhausen, Switzerland FEI# 3002646188	Econazole Nitrate/61W[]S44 11/02/00 Mefloquine HCl/62L[]S30 11/02/00 Methimazole/66K[]S01 11/2/00
Ckdt Communications Ag 118 Lettenweg Allschwil, Switzerland FEI# 3001221928	Clozapine/65V[]S13 11/02/00 Thiorodazine/66M[]S60 11/2/00
Deltrachem Trading Ag Brisenstrasse 9 Stans, Switzerland FEI# 3000313481	Indomethacin/62G[]S42 11/02/00
Dolder Ag Immengasse 9 Basel, Switzerland FEI# 1000393094	Furazolidone/62F[]S13 11/02/00 Minoxidil/62C[]S41 11/02/00 Naphazoline HCl/60C[]S46 11/02/00 Nitrofurazone/62F[]S29 11/02/00
Hoffman La Roche, Ltd. Grenzacherstrasse 124 Basel, Switzerland FEI# 3002807200	Flucytoisine/61W[]S10 11/02/00 Fluorouracil/62I[]S23 11/02/00 Nicardipina HCl/620[]S48 11/02/00 Flunisolide/Flunisolide Hemihyrate 62G[]S35, 62L[]S26 11/02/00
Orgamol Unknown Street Evionnaz, Switzerland FEI# 3002134046	Bupivacaine HCl/Bupivacaine 60Q[]S30 11/02/00 Diethylpropion HCl/60R[]S07 11/02/00 Ribavirin/62V[]S12 11/02/00
Orgamol Fabrication 1092 Evionnaz Geneva, Switzerland FEI# 3001677591	Bupivacaine/60Q[]S30 11/02/00 Diethypropion HCl/60R[]S07 11/02/00
Siegfried CMS 4800 Zofingen Schweiz, Switzerland FEI# 3001657741	Allopurinol/66T[]S01 11/02/00
Siegfried CMS Unt. Bruhlstrasse 4 Zofingen, Switzerland	Allopurinol/66T[]S01 11/02/00

FEI# 3002808158

Sigamed Ag Ltd Ch6300 Zug Schweiz, Switzerland FEI# 3002566273	Phenazopyridine HCl/60L[]S82 11/02/00 Primidone/61M[]S25 11/02/00

TAIWAN, REPUBLIC OF CHINA (TW)

Everlight Chemical Industrial Corporation No. 77 Tun Hua South Road Taipei, Taiwan FEI# 1000537285	Misoprostol/65K[]S09 11/02/00
Sunstar Chem & Pharm.Corp. 319, Kai Yuen Road Hsin-Ying, Taiwan FEI# 1000388232	Chlorzoxazone/65Q[]S31 11/02/00
Tong Sing Chemicals Co Ltd 6f 45 Kirin Rd Taipei, Taiwan FEI# 1000174712	Diclofenac Postassium/62G[]S18 11/2/00 Diclofenac Sodium/62G[]S18 11/02/00

THAILAND (TH)

Lupin Chemicals 71 Sap Rd.Siphaya Bangkok, Thailand FEI# 3001261914	Pyrazinamide/61H[]S27 11/02/00

TURKEY (TR)

Atabay Kimya San. Ve Tic. A.S Acibadem Koftunku Sok. No. 1 Istanbul, Turkey FEI# 1000315153	Metformin HCl/61P[]S26 11/02/00
Atabay Kimya Sanayi Acibadem Koftuncu No 1 Istanbul, Turkey FEI# 3002765257	Metformin HCl/61P[]S26 11/02/00
Atabay Kimya Sanayi Acibadem Koftuncu Sokak No 1 Kadikoy Istanbul, Turkey FEI# 3002303805	Metformin HCl/61P[]S26 11/02/00

UNITED KINGDOM (GB)

Abbott Laboratories Whiteway Queenborough, United Kingdom FEI# 768	Vancide/61S[]S99 11/02/00
Archimica Ltd. Sandycroft,Deeside Flintshire, United Kingdom	Isosorbide Dinitrate/66S[]S24 11/02/00

FEI# 3002686934

Glaxco Wellcome Export Limited Priory Street Herts, United Kingdom FEI# 1000404000	Vlalciclovir HCl/62V[]S99 11/02/00 Cisatracurium Besyate/ 65Q[]S59 11/02/00
Glaxco Wellcome Export Ltd. Temple Hill Dartford, United Kingdom FEI# 1000403198	Mercaptopurine/62I[]S30 11/02/00 Cisatracurium Besyate/ 65Q[]S59 11/02/00
Micron Technologies 8 Leesons Hillst Pauls Cray Orpington, United Kingdom FEI# 3000230960	Sulfabenzamide/61G[]S43 11/02/00
Morphun Plc 7 Chesterfield Road Chiswick, London, England, United Kingdom FEI# 3002614351	Haloperidol/66M[]S36 11/02/00
Quntiles Scotland Limited Inchwood Bathgate W. Lothian, United Kingdom FEI# 3001084653	Naproxen/62G[]S49 11/02/00
Rhone Poulenc Agriculture Fyfield Road Ongar Dagenham, United Kingdom FEI# 1000176968	Acebutolol/Acebutolol HCl/ 60X[]S15 11/02/00
Robinson Bros Ltd Charles St West Bromwich W Midlands, United Kingdom FEI# 1000202202	Fluoxetine/61N[]S29 11/02/00
Rosemont Pharmaceuticals Ltd Rosemont House Yorkdale Industr. Park Leeds, United Kingdom FEI# 3002442738	Chlorpromazine HCl/61T[]S04 11/02/00
Seaweld Divers Ltd. The Limes The Street Acle Norwich Norfolk, United Kingdom FEI# 1000654750	Oxandrolone/60N[]S09 11/02/00
Gerald Wise & Co Ltd 225a Finchley Road London, United Kingdom FEI# 1000163913	Nicotine Polacrilex Resin/ 66V[][]99, 55R[][]99 11/02/00
Wyeth Ayerst Research 154 Fareham Rd. Gosport Hants, United Kingdom FEI# 3001270580	Acetazolamide/63D[]S01 11/02/00

Wyeth Laboratories U K New Lane Havant Hampshire, United Kingdom FEI# 1000269463	Acetazolamide/63D[]S01 11/02/00
Zeneca Pharmaceuticals Ltd Alderly Park, Macclesfield Cheshire, United Kingdom FEI# 3001561876	Meropenemici/61G[]S80 11/02/00 Propranolol HCl/63E[]S13 11/02/00